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New guanidinium-based carboxylate receptors derived from 5-amino-pyrrole-2-carboxylate: synthesis and first binding studies

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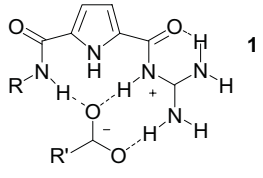
Abstract—The syntheses of two new guanidinium-based carboxylate receptors **2a**,**b** derived from 5-amino pyrrole-2-carboxylate **4** are described. These receptors bind *N*-acetyl alanine carboxylate and *O*-acetyl lactate efficiently in aqueous DMSO as could be shown by NMR studies. However, compared to previously reported guanidiniocarbonyl pyrrole receptors **1**, the reversal in the direction of the amide group in **2a**,**b** changes both the substrate selectivity (amides are now preferred over esters) and their relative binding affinities. Both effects can be explained based on the calculated complex structure.

The binding of anions in polar solutions is an important aspect of today's supramolecular chemistry.[1] Artificial anion receptors can function as sensors for the detection of environmentally critical analytes or as model systems to study the binding of small anionic biomolecules by natural anion receptors such as proteins or enzymes. The latter aspect is especially appealing as a variety of interesting biomolecules can be anionic such as DNA, amino acids,[2] peptides[3] and proteins or carbohydrates. In these cases, ionic interactions, for example, the formation of ion pairs is very often crucial for the selective complexation of anions in polar solvents.[4] However, this primary interaction is normally fine-tuned by additional attractive or repulsive interactions to increase substrate selectivity.



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We are currently studying the complexation of amino acid carboxylates by guanidiniocarbonyl pyrrole cations **1**.[2a–c,5,6] Due to the increased acidity caused by the acylation and the additional H-bonds, the binding is much more efficient compared to simple guanidinium cations.[5] But, so far, we have only investigated receptors derived from pyrrole-2,5-dicarboxylic acid. We have now prepared a new class of amino acid receptors **2** based on 5-amino-pyrrole-2-carboxylate **4** in which the direction of the amide group in position 5 at the pyrrole is reversed. This exchange of H-bond donor and acceptor could have interesting effects on either the stability or the selectivity of such receptors. We want to present here the syntheses of two prototypes **2a**,**b** and preliminary binding studies using both *N*-acetyl alanine **18** and *O*-acetyl-lactate **19** as substrates.

The synthesis of these two new compounds proved to be more difficult than initially expected. Our first attempt was based on our previous strategy for the synthesis of the pyrrole dicarboxylic acid based receptors **1** (Scheme 1).[5] Nitration of pyrrole carboxylic acid should provide after reduction the 5-amino-pyrrole-2-carboxylic acid ester **4**. The free amino group in **4** could then be reacted with any acyl chloride, for example, to give the acylated esters **3**. The pyrrole carboxylic acid obtained after hydrolysis thereof could then be coupled with *t*-Boc-guanidine **13** to give the desired receptors **2** after deprotection.

However, the direct nitration of pyrrole-2-carboxylic acid ester **6** in position 5 was rather low yielding (Scheme 2). Besides only 10% of the desired 5-amino

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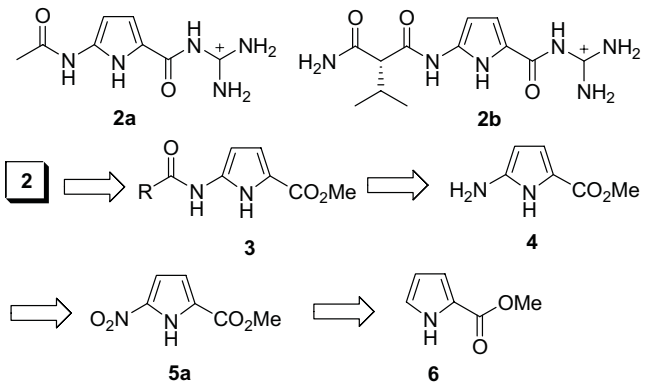
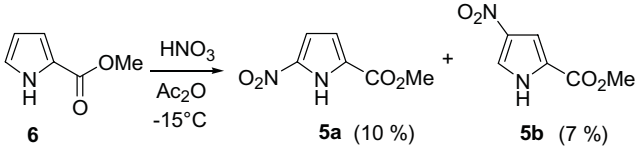


Scheme 1. Retrosynthesis for the new amino acid receptors of type **2**.

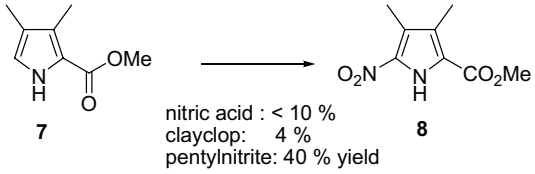


Scheme 2. Direct nitration of **6** gives a mixture of the two regioisomers **5a** and **5b** in low overall yields.

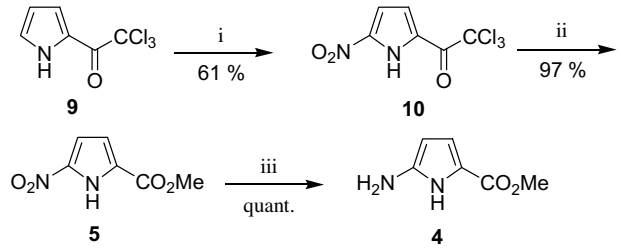
derivative **5a** also 7% of the unwanted 4-amino pyrrole **5b** were isolated. The general problem of the synthesis of nitro pyrroles is their decomposition most likely due to oxidation under the reaction conditions.[7] In accordance with this, only modest yields varying from 10% to 30% are reported in the literature for such reactions.[8] And the more efficient reactions are normally only observed in the case of N-alkylated or acylated pyrroles. Another problem besides the low yields in general is the regioselectivity, which favours substitution in position 5 of a 2-acceptor substituted pyrrole only under kinetic conditions whereas under thermodynamic control substitution in 4 position is preferred.[9] Due to the electron withdrawing carboxyl group in the starting material, the reaction is unfortunately very slow under kinetic conditions (e.g. low temperature).

We tried to circumvent both problems by using 3,4-dimethyl-pyrrole-2-carboxylic acid **7** as the starting material (Scheme 3). In **7**, the methyl groups not only block the 3 and 4 positions but also increase the electron density in the pyrrole making it in principle more susceptible for nitration, but obviously unfortunately also for oxidation and decomposition. When we tested different nitrating reagents such as nitric acid,[8] 'claycop'[10] and *n*-pentylnitrite[11] under different reaction conditions by varying the temperature and concentrations, the yields of the desired nitro pyrrole **8** were 40% at best besides significant amount of decomposition.

We finally succeeded in preparing the desired 5-nitro-pyrrole-2-carboxylate **5** by direct nitration of the trichloroacetylated pyrrole **9** (Scheme 4).[9] Reaction of **9** with nitric acid and Ac_2O at −40 °C provided the 5-nitro regioisomer **10** as the major product with 61% yield. Under similar reaction conditions pyrrole carboxylic ester **6**



Scheme 3. Direct nitration of **7** using various reagents and conditions.

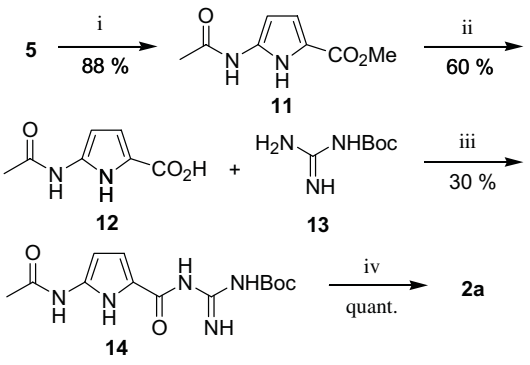


Scheme 4. Synthesis of 5-amino pyrrol-2-carboxylate **4**. Reagents and conditions: (i) HNO_3, Ac_2O, −40 °C; (ii) MeONa, MeOH, reflux; (iii) H_2, Pd/C, MeOH.

gave **5a** in only 10% yield (Scheme 2). After basic hydrolysis of the trichloroacetyl group the nitro group in **5** was then successfully reduced with hydrogen (Pd/C) to give the desired 5-amino-pyrrole-2-carboxylic acid methyl ester **4**.

Amino pyrrole **4** was then used to prepare two prototypes of our new receptor class, the acyl derivative **2a** and the valine derivative **2b**. For the acyl derivative **2a**, amino pyrrole **4** obtained after the reduction of nitro pyrrole **5** was directly reacted without further purification with Ac_2O in chloroform at 60 °C to give the acetamido pyrrole **11** in good yields of 88% (Scheme 5). After hydrolysis of the methyl ester with lithium hydroxide in methanol at 60–80 °C, pyrrole carboxylic acid **12** was coupled with *t*-Boc-guanidine **13** using PyBOP as the coupling reagent. After cleavage of the *t*-Boc-protecting group in **14** with TFA in dichloromethane the acetyl receptor **2a** was isolated as the picrate salt.

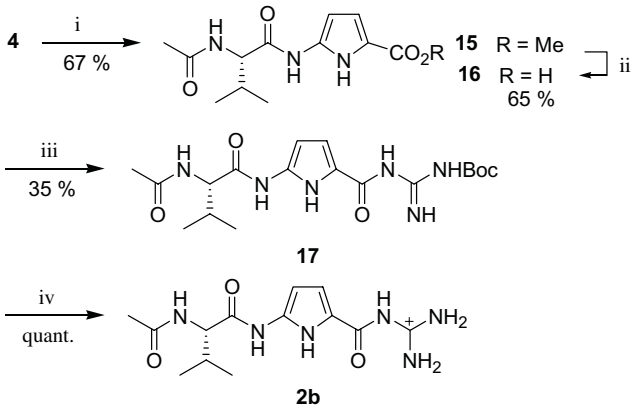
For the valine derivative **2b**, the amino pyrrole **4** was reacted with N-Ac-Val-OH **20** using DCC, HOBT and



Scheme 5. Synthesis of the acetyl receptor **2a**. Reagents and conditions: (i) 1. H_2, Pd/C, MeOH, rt, 2. Ac_2O, $CHCl_3$, 18 h, 60 °C; (ii) LiOH, MeOH, 80 °C; (iii) PyBOP, NMM, DMF, rt; (iv) TFA.

DMAP in a mixture of DMF and dichloromethane (1:1) to obtain **15** in good yields of 67%. Similar to the synthesis of **2a**, the methyl ester was hydrolyzed (NaOH) and the free acid coupled with *t*-Boc-guanidine (**13**). Deprotection (TFA) provided the valine receptor **2b** (isolated as the picrate salt) (see Scheme 6).

After successful synthesis of these two prototypes **2a** and **2b**, their complexation properties were first probed qualitatively by NMR studies in 40% H_2O in DMSO. Upon the addition of N-Ac-*L*-Ala-O^- (NMe_4^+-salt) **18** to a solution of **2a** significant complexation induced shift changes for protons of both substrate and receptor are observed (Fig. 1) indicating a molecular interaction between anionic guest and cationic receptor in this solvent mixture.[12]



Scheme 6. Synthesis of the valine receptor **2b**. Reagents and conditions: (i) 1. H_2, Pd/C, MeOH, rt, 2. **20**, DCC, HOBT, DMAP, CH_2Cl_2, DMF; (ii) NaOH, MeOH, rt; (iii) **13**, PyBOP, NMM, DMF, rt; (iv) TFA.

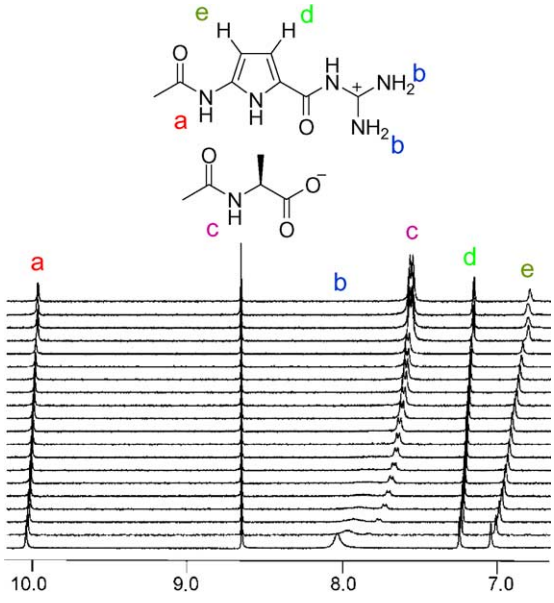


Figure 1. Parts of ^1H NMR spectrum of **2a** and *N*-Ac-*L*-Ala-O^- (NMe_4^+-salt) in 40% water in DMSO-d_6.

We then performed quantitative NMR titration studies. Aliquots of the amino acid carboxylate **18** (NMe_4^+-salt) were added to a solution of receptor **2a** (picrate salt, [**2a**] = 1.5 mM) in 40% water in DMSO-d_6. The NMR spectrum was recorded after each addition and from the observed shift changes the binding constant can be calculated using a nonlinear curve fitting procedure for a 1:1-complexation model (Fig. 2).[12] The complex stoichiometry was independently confirmed by a Job-plot (Fig. 3).[13] In the same way, the binding of **18** to the valine receptor **2b** (1.5 mM) was studied. Furthermore, *O*-acetyl lactate **19** was studied as a substrate for both receptors. The corresponding association constants as obtained from these NMR titration experiments are summarized in Table 1.

With association constants ranging from $K = 220$ to 460 M^{-1} both receptors bind the two carboxylates quite efficiently in aqueous DMSO. Interestingly, compared to our previous receptors of type **1**,[5] which bind lactate better than alanine carboxylate, the substrate selectivity is now reversed. Especially, the acetyl receptor **2a** binds alanine significantly better than lactate. Hence, the new

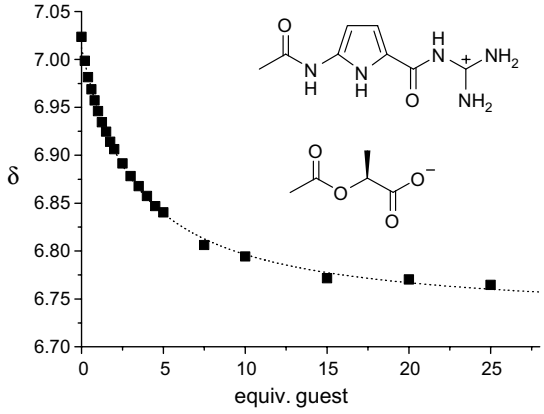


Figure 2. Binding isotherm for the complexation of *O*-acetyl lactate **19** by the acetyl receptor **2a** in 40% water in DMSO-d_6 (shift change of the pyrrole CH).

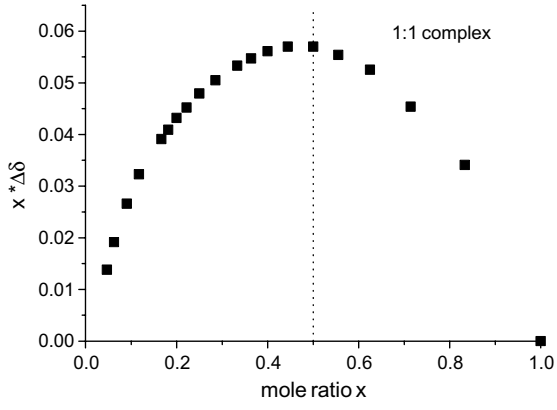


Figure 3. NMR based Job plot for the complexation of N-acetyl alanine carboxylate **18** by the valine receptor **2b** in 40% water in DMSO-d_6 proving the 1:1-complex stoichiometry.

Table 1. Association constants for **2a** and **2b**

	N-Ac-*L*-Ala-O$^-$ (NMe_4^+-salt) **18**	*O*-Ac-*L*-Lac-O$^-$ (NMe_4^+-salt) **19**
2a	460 M^{-1}	220 M^{-1}
2b	320 M^{-1}	270 M^{-1}

amino pyrrole based receptors **2** prefer amides over esters. Another noteworthy observation is that the acetyl receptor **2a** binds alanine more efficiently than the valine receptor **2b**, which is also in contrast to our previous receptors **1** where the association constants for the analogous valine derivative were close to three times larger than those of simple alkyl amide receptors. Hence, the change of the direction of the amide group going from **1** to **2** significantly affects both the substrate selectivity (amide vs ester) and the relative binding affinities of these receptors (**2a** vs **2b**).

The energy minimized structure (Macromodel 8.0, Amber*, GB/SA water solvation, Monte Carlo search with 50.000 steps)[14] of the complex between the acetyl receptor **2a** and alanine carboxylate **18** shown in Figure 4 offers a possible explanation for these two effects, the changes both in substrate selectivity and relative receptor affinities: As in complexes with receptors of type **1**, the carboxylate forms a H-bond enforced ion pair with the guanidiniocarbonyl pyrrole moiety of **2**. Furthermore, the CO of the reversed amide can now form an additional H-bond to the amide NH of the substrate as also supported by the observed complexation induced shift changes in the NMR (Fig. 1). This explains the preference for amides over esters. This interaction, however, brings the two acetyl groups of the substrate and the receptor into close proximity. Any larger group at this position of the receptor such as the valine substituent in **2b** probably leads to destabilizing steric interactions with the substrate. Hence, the binding affinity of **2b** is smaller than that of **2a**.

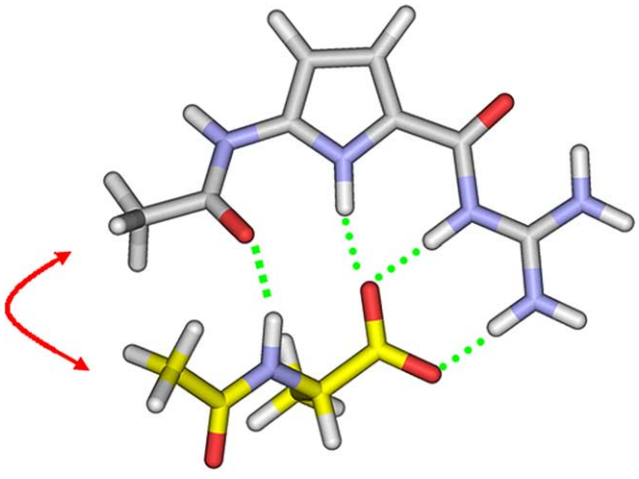


Figure 4. Calculated energy minimized structure for the complex between **18** (yellow) and **2a** (grey). Hydrogen bonds are shown in green, unfavourable steric interactions in red.

Conclusion: We have shown here how the reversal of the direction of an amide group in 5-amino substituted guanidiniocarbonyl pyrrole receptors **2** changes both substrate selectivity and relative binding affinities. We are now exploring the scope of this new receptor class for the selective binding of dipeptides over depsipetides.

Acknowledgements

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Supplementary data

Details of the synthesis of receptor **2a** and **2b**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.08.115.

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