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[c003]

STUDIES ON THE USE OF NAPHTYRIDINE DERIVATIVES AS EFFECTIVE RECEPTORS

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Abstract

The association constants K_b of three receptors (**I**-**III**), designed to have both enhanced hydrogen bonding donor strength and conformational preorganization, with biotin analogues (**1**-**5**) are reported. ^{1}H-NMR titrations using the saturation conditions have been employed to determine the association constants K_b.

Introduction

Amide N-*H* groups have been used to produce a wide range of receptors capable of coordinating biologically important molecules and anions.[1,2] General reviews covering anion receptors containing amide groups have been recently published.[3,4]

Due to their unique stereoelectronic character, they interact with electron deficient centres through the carbonyl group and with electron rich centres through N-*H* units; this dual feature has been successfully used for the design of amide-based receptors able to recognize a large variety of guests. On the other hand the recognition capabilities of fused-pyridine and naphthyridine receptors remains an important challenge of supramolecular chemistry.[5]

Our previous works have been focussed towards the design, synthesis and host-guest behaviour of different receptors using biotin methyl ester (**1**).[6-11] Here we turned our attention to modifications on the latter molecule by comparatively studying a series of 4*S*-substituted (3a*R*,6a*S*)-tetrahydro-1*H*-thieno[3,4-d]imidazol-2(3*H*)-ones (**2**-**4**).

Results and discussion

This communication will report the measurement and analysis of the binding constants, K_b of five guests (**1**-**5**) with three receptors, 3,4,5,6-tetrahydro-3,3,6,6-tetramethylenebis-(pyrido[3,2-g]indolo)[2,3-*a*:3´,2´-*j*]acridine (**I**),[6] *N*,*N'*-bis(7-methyl-1,8-naphthyridin-2-yl)-1,3-benzenedi-carboxamide (**II**),[6] and *N*,*N'*,*N''*-tris(7-methyl-1,8-naphthyridin-2-yl)-1,3.5-benzenetricarboxamide (**III**) [8] (Figure 1).

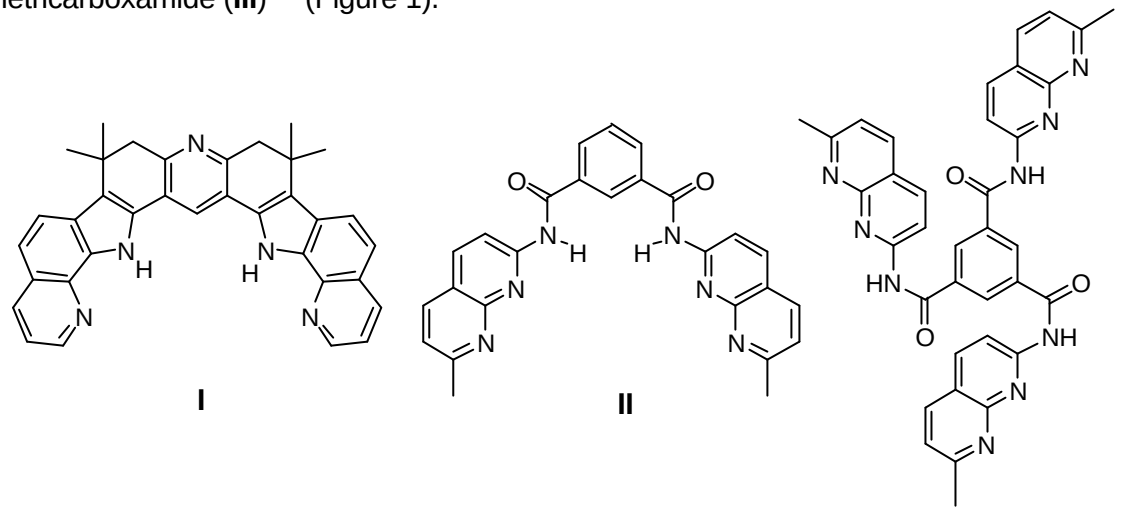

Figure 1. Receptors (**I**-**III**).

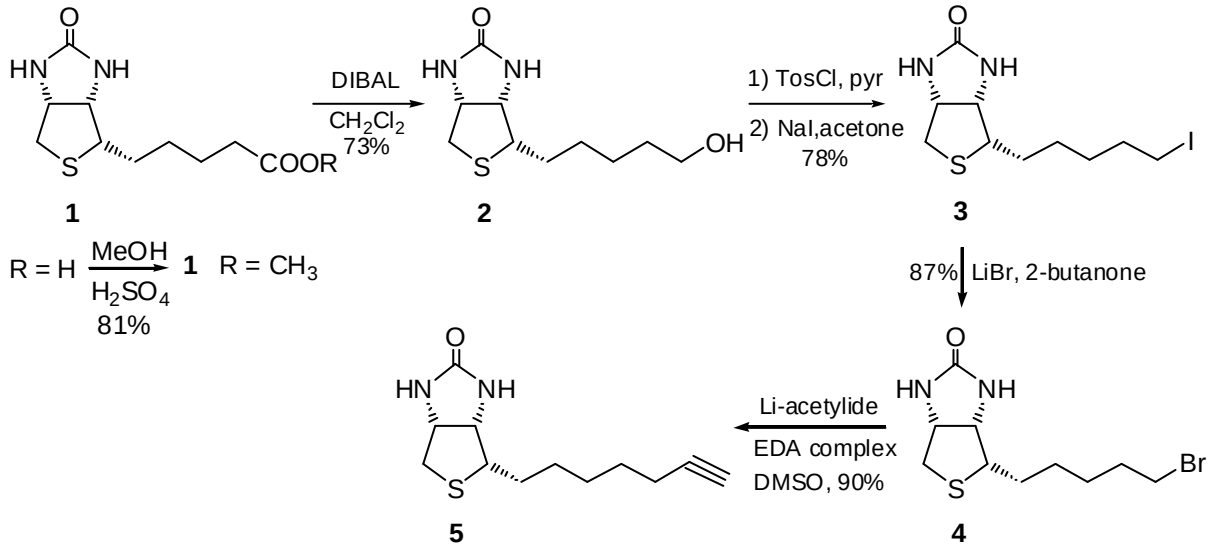

Figure 2. The 4*S*-Substituted (3a*R*,6a*S*)-tetrahydro-1*H*-thieno[3,4-*d*]imidazol-2(3*H*)-ones (**1**-**5**).

Guests **1**[12] and **2-5**[13] were synthesized according to described procedures with slight variations (Figure 2). The first step was the preparation of biotin methyl ester **1** by acid-catalyzed esterification of biotin. Selective reduction of **1** using DIBAL at -78 ºC affords alcohol **2** in 73% yield. The iodide **3** was prepared from biotin tosylate by halide substitution with NaI in acetone. The reaction of **3** with LiBr in 2-butanone results in the formation of bromide **4** in 87% yield. Finally, alkyne **5** was obtained by substitution reaction of bromide **4** with lithium acetylide-ethylenediamine in DMSO at 15 ºC in high yield.

The ability of receptors containing pyridine or naphthyridine moieties **I**-**III** to recognize and bind the aforementioned guests can be evaluated using ^{1}H-NMR spectroscopy. The stoechiometry of the complexes must be determined beforehand to use the right equations on the titrations. We have used the method of continuous variation to generate Job plots by preparing different mixtures of receptor and guest covering the whole range of molar fractions of the receptor but keeping constant the total concentration of the solutions. The plot of the product between the increment in the chemical shift and the receptor concentration versus the molar fraction of the receptor affords a curve, from the value of the maximum, which can be obtained by means of equation $X = m/(m+n)$,[14] the stoechiometry of the complex can be determined. For all the compounds used in this study we always obtained a 1:1 stoechiometry.

Binding Studies

Association constants K_b for receptors **I**-**III** with biotin derivatives **1**-**5** as guests were determined by ^{1}H-NMR titration experiments in $CDCl_3$ using the EQNMR software to fit the curves to a 1:1 binding model (Table 1).[15]

Table 1. Association constants K_b (M^{-1}) for **I**-**III** binding **1**-**5** measured at 300 K in $CDCl_3$ (Errors < 10%)

Comp.	1	2	3	4	5
I	2700	-[b]	1500	2000	1900
II	67000	-[b]	5600	6020	4700
III	250000 100[a]	-[b] 110[a]	800	1700	1000

[a] with 10% of MeOD, [b] not detected

The values have been calculated from the chemical shift induced effects on the N-*H* groups of receptors **I**-**III**.

Addition of guests (**1**-**5**) to **I**-**III** in $CDCl_3$ results in downfield shifts of the N-*H* groups of receptors (**I**-**III**), due to hydrogen bonding interactions. The selectivity displayed by all three receptors **I**-**III** is similar to the trend CO_2Me >> Br = I = acetylide (Figure 3).

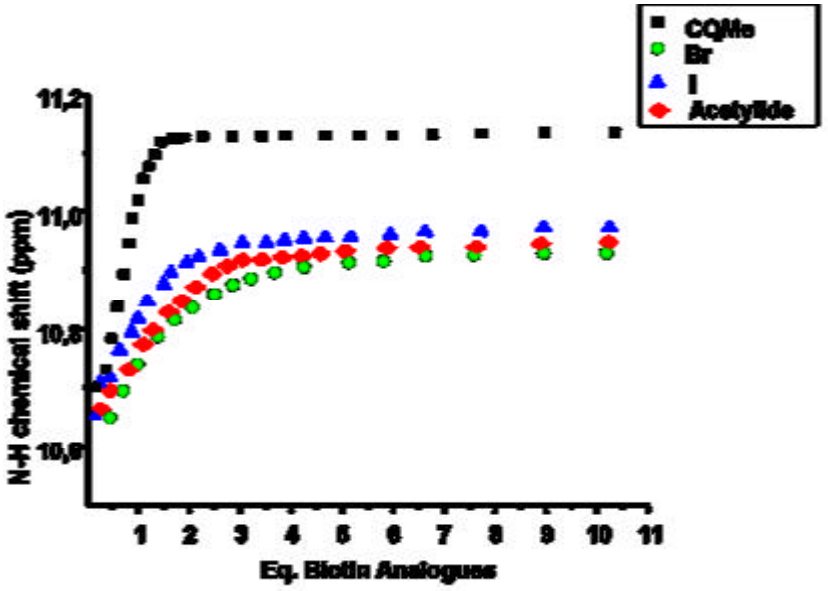

Figure 3. N-*H* chemical shift variations in receptor **III** as function of the equivalents of added guest.

The receptors **II** and **III** have high association constants with biotin methyl ester (**1**), $6.7 \cdot 10^4$ and $2.5 \cdot 10^5$ M^{-1}, presumably due to the formation of additional hydrogen bonds with the receptors involving the methyl ester group that could further stabilize the complex. In addition, the biotin analogues with bulky groups (Br, I and acetylide) will destabilize the complex due to steric repulsion and that seems to be the most important factor influencing the relative poor association constants obtained for these guests.

Guest **2** was insoluble in $CDCl_3$, therefore in order to be able compare its behaviour with that of the other guests, the ^{1}H-NMR titration was achieved in a 10% MeOD-90% $CDCl_3$ solution. As control the biotin methyl ester (**1**) was titrated in the same conditions with receptor **III**. The obtained association constants K_b were: 100 M^{-1} for **1** and 110 M^{-1} for **2**, suggesting that the latter guest interacts with receptor **III** in a similar manner as it does **1**. On the contrary, guest **2** does not interact with receptors **I** and **II**. The modification of the alkyl chain of biotin, has not an effect on the association constant.

Conclusions

The naphthyridine receptors **II** and **III** exhibit a high selectivity towards the biotin methyl ester (**1**), due to the stabilization of the complex by additional hydrogen bonds, with an association constant K_b = $6.7 \cdot 10^4$ and $2.5 \cdot 10^5$ M^{-1} respectively in $CDCl_3$. These studies illustrate the capability to modulate the association constant of receptors depending on the biotin type analogue. We have found that the selectivity follows the sequence: OH ~ CO_2Me >> Br = I = acetylide.

Acknowledgments

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