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Chiral enantiopure bis(thio)ureas derived from TADDOL and their carboxylate complexation capacity

Research Article

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Abstract: New chiral enantiopure ureas and thioureas with (*R,R*)-TADDOL backbone were synthesized. Bis-(thio)ureas with C2 symmetry were obtained from TADDOL iso(thio)cyanates and bifunctional amino-(thio)ureas from TADDAMINE, respectively. These were tested for carboxylate recognition capacity and the association constant was determined for the most stable complex.

Keywords: *TADDOL • Enantiopure (thio)urea • Carboxylate recognition*

1. Introduction

Chiral (thio)ureas and amino(thio)ureas have found many applications in organocatalysis [1-4] and molecular recognition [5-8].

The success of the recognition process depends on two factors: hydrogen bonding due to the acidity of the NH protons and the topology of the binding site. Ureas and thioureas are some of the best receptors for Y-shaped oxoanions, such as carboxylates [5,9-11]. One noticeable application is the enantioselective molecular recognition of carboxylate group of aminoacids when the (thio)urea receptor is chiral. The ability of these compounds to recognize carboxylate anions is due to a double hydrogen bonding formation between the carboxylate group and the two hydrogen atoms of the receptor. Even though most of the time thioureas have better complexation capacity compared to their oxygenated analogs due to the higher acidity of the NH found in the former, the difference in orientation, *syn* or *anti*, of the two acidic protons can favor the ureas, as previously reported by our group [8]. TADDOLs are extraordinary versatile chiral auxiliaries [12-14] derived from tartaric acid. Bis-amino analogues of TADDOLs: TADDAMINEs have been far less studied and, to the best of our knowledge, ureas and thioureas derived from TADDAMINEs have not been reported. Aiming to take advantage of the TADDOL backbone properties and our experience in working with these diols [15], we started to prepare a library of chiral (thio)urea hosts to evaluate their anion recognition capacity [16].

2. Experimental procedure

Chemicals were obtained from commercial suppliers and used without further purification. The acetonitrile used for the UV-Vis titrations was purified by distillation from calcium hydride, in an inert atmosphere. All the new compounds were characterized and their preparations are described in the supplementary material. Melting points were determined on a Boëtius hot plate and are uncorrected. The measurements of optical rotation were performed on a 241 Perkin Elmer polarimeter using a quartz cell with the length of 1 dm. The NMR spectra were recorded on a BRUKER Avance 400 NANO (400 MHz for ^{1}H) in deuterochloroform ($CDCl_3$) at room temperature. The chemical shift (δ) values are given in ppm, tetramethylsilane (TMS) was used as an internal standard. The High Resolution Mass Spectra (HRMS)

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were measured on a QStar Elite (Applied Biosystems SCIEX) spectrometer equipped with a time-of-flight (TOF) detector. UV-Vis spectra were recorded on a Shimadzu UV-2401PC using a quartz cell with the length of 1 cm. For the acquisition and treatment of the UV-Vis spectra a UV Probe version 2.0 from Shimadzu was used.

3. Results and discussion

3.1. Synthesis of the chiral selectors

The chiral thioureas and ureas were obtained by the nucleophilic addition of an amine to isothiocyanates and isocyanates, respectively [17]. There are two possible approaches for this synthesis: either using an iso(thio) cyanate derived from TADDOL 1 and a commercially available amine, or using TADDAMINE 2 (the primary amine derived from TADDOL) with commercially available iso(thio)cyanates.

We first synthesized the (*R,R*) TADDOL 1 as previously reported [18]. From TADDOL 1, in a two step synthesis we obtained the isothiocyanate 3a using Seebach's procedure [19,20]. (*S,S*) TADDAMINE 2 was synthesized from (*R,R*) TADDOL 1 in a classic three step synthesis [19]. The isocyanate 3b was obtained by carbonylation of the TADDAMINE 2 with triphosgene, $(CCl_3O)_2CO$, in dichloromethane. The reaction takes place with a quantitative yield at room temperature.

For the synthesis of *bis*-(thio)ureas we have chosen the first approach: the reaction of amines with compounds 3a or 3b as presented in Scheme 1. When diethylether is used as a solvent the reaction product precipitates and can be isolated in very high purity by a simple filtration. Results for the synthesis of *bis*-thioureas and *bis*-ureas are summarized in Table 1.

Very good yields (94-98%) are obtained when using aliphatic amines. For instance, *bis*-thioureas with R = methyl H1, isopropyl H2 and benzyl H3 were obtained from isothiocyanate 3a in 94%, 97% and 98%, respectively, while the corresponding urea with R = isopropyl H4 was formed in 96% yield from isocyanate 3b. Unfortunately, the use of aromatic amines did not match the same success rate. Even under more energetic conditions, such as microwave irradiation, reflux in acetonitrile or toluene, or in the presence of various catalysts (DMAP, DBU, $LiClO_4$) the reaction between iso(thio)cyanates 3 and aromatic amines did not succeed; we could recover the unreacted iso(thio) cyanate 3.

For the amino-(thio)ureas we used an alternative pathway, involving TADDAMINE 2 and aromatic iso(thio)cyanates (Scheme 1). The synthesis of amino-

Table 1. Synthesis of the hosts.

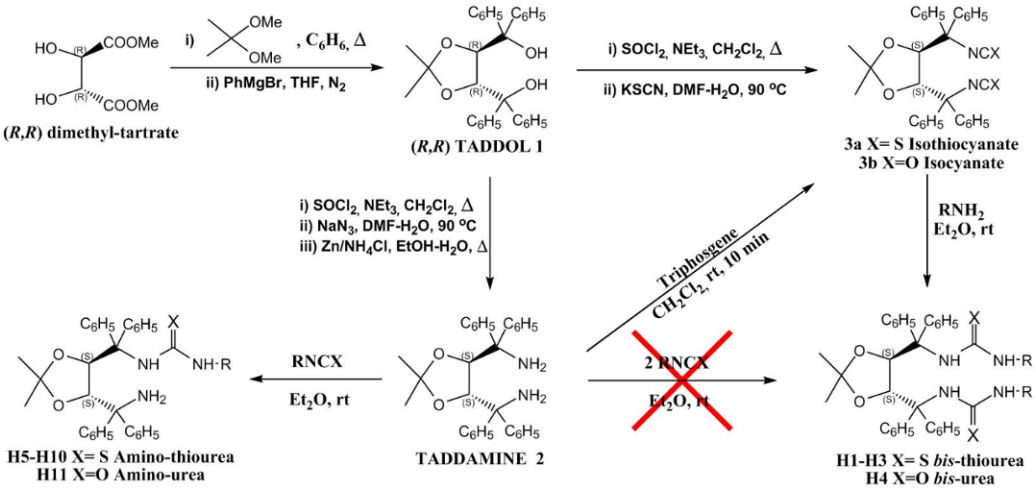
Entry	X	R	Yield (%)	Host
Bis(thio)ureas				
1	S	Me	94	H1
2	S	iPr	98	H2
3	S	Bn	97	H3
4	O	iPr	96	H4
Amino-(thio)ureas				
5	S	Me	89	H5
6	S	Ph	98	H6
7	S	4-NO_2-Ph	95	H7
8	S	4-Cl-Ph	95	H8
9	S	3,5(CF_3)Ph	84	H9
10	S	iPr	90	H10
11	O	Ph	99	H11

hosts H5-H11 was performed at room temperature in diethylether. The product could be isolated after three hours in very high yields (84-99%). With aliphatic isothiocyanates, such as methyl and isopropyl, the reaction time was longer (up to 3 days) due to their lower electrophilicity. Moreover, the reaction of TADDAMINE 2 with 2 equivalents of isothiocyanates, even in the same energetic conditions, stopped at amino-thioureas and the *bis*-thioureas were not obtained. These results are also presented in Table 1. We obtained six thiourea derivatives with various substituents, as well as, for the sake of comparison, one urea derivative.

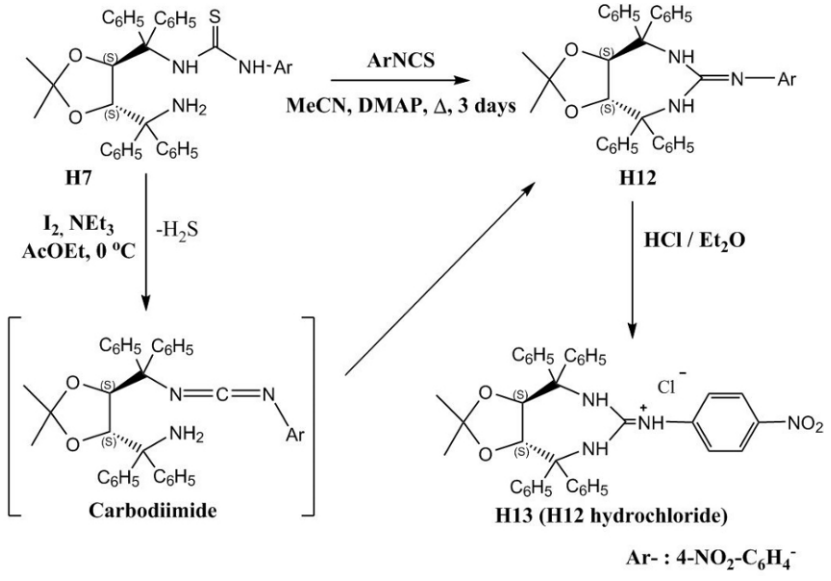
Interestingly enough, prolonged heating of TADDAMINE 2 with some aromatic iso(thio)cyanates, at reflux in acetonitrile leads to the formation of guanidine derivatives. For example, heating for 3 days the host molecule H7 with two equivalents of 4-nitrophenyl isothiocyanate, in the presence of DMAP, yielded guanidine derivative H12; 4-nitroaniline was formed as a by-product. The guanidine can be obtained through a more elegant (and shorter) two-step, one-pot pathway from TADAMINE 2. In the first step a carbodiimide is formed by dehydrosulfuration of H7, which takes place in the presence of iodine and triethylamine in ethylacetate at 0°C [21]; the second step yields the guanidine through intramolecular addition of the free amino group to the carbodiimide, at room temperature. The guanidine hydrochloride is finally separated by precipitation with hydrochloric acid from diethylether solution. Since guanidines and their salts can also be used as hosts for the molecular recognition of carboxylates [22] we added these two compounds (guanidine H12 and its hydrochloride H13) to our library.

3.2. Complexation study by UV-Vis titration

The carboxylate complexation is an equilibrium process between the host molecule H (*bis*-thioureas, *bis*-ureas and guanidines H1-H13) and the guest G



Scheme 1. Synthesis of host molecules H1-H11.



Scheme 2. Synthesis of guanidine H12 and guanidine hydrochloride H13.

(the carboxylate) in a polar solvent, with the formation of a complex C. The process is characterized by its association (or binding) constant, *K*, which represents the ratio of the concentrations of the complex [C] and the free species [H] and [G] at equilibrium:

$$a\,\mathbf{H} + b\,\mathbf{G} \underset{}{\overset{K}{\rightleftharpoons}} \mathbf{C} \qquad K = \frac{[\mathbf{C}]}{[\mathbf{H}]^a \times [\mathbf{G}]^b}$$

The progress of the complexation process was observed through UV-Vis spectroscopy, due to the simplicity and fast response of this method. Moreover, this technique uses small quantities of host and guest molecules (10^{-4}-10^{-6} M solutions of the two partners).

The chosen partner molecules were H7 as the host and tetra-*n*-butylammonium acetate (TBAA) as guest. We attempted the complexation in three different solvents: acetonitrile, dimethyl sulfoxide and dichloromethane. As observed in the absorption spectra, the complexation occurred in the first two solvents, while in dichloromethane no change was recorded in the UV spectra, even after adding increments of TBAA solution. The experiments were performed by adding 50, 200 and 600 µL of a 2×10^{-3} M solution of TBAA guest to 100 µL, 5×10^{-4} M, solution of H7 host in 1.9 mL of solvent. In this case we used a host/guest ratio of 1:2, 1:8 and 1:24.

After selecting acetonitrile as solvent of choice, we tested the rest of the library (ureas, thioureas and guanidines) in the same conditions as presented above. The results are presented in Table 2.

UV-Vis spectra are useful for following up the complexation process. For instance, for H7 we observed a bathochromic effect, its characteristic absorption band

Table 2. Complexation study with TBAA in acetonitrile at H : G ratio of 1:24.

Entry	Host		R	λ_{max} (nm) free host	λ_{max} (nm) complex
1	H1	*Bis-thiourea*	Me	251	-
2	H2	*Bis-thiourea*	iPr	255	-
3	H3	*Bis-thiourea*	Bn	255	-
4	H4	*Bis-urea*	iPr	255	-
6	H5	*Amino-thiourea*	Me	-	-
7	H6	*Amino-thiourea*	Ph	242	-
8	H7	*Amino-thiourea*	4-NO_2-Ph	348	468
9*	H7	*Amino-thiourea*	4-NO_2-Ph	366	489
10**	H7	*Amino-thiourea*	4-NO_2-Ph	304 & 333	-
11	H8	*Amino-thiourea*	4-Cl-Ph	247	-
12	H9	*Amino-thiourea*	3,5(CF_3)Ph	280	314
13	H10	*Amino-thiourea*	iPr	253	-
14	H11	*Amino-urea*	Ph	243	-
15	H12	*Guanidine*	4-NO_2-Ph	354	375
16	H13	*Guanidine HCl*	4-NO_2-Ph	356	381

** solvent – DMSO; ** solvent – dichloromethane*

Table 3. Absorbance of the complex measured for different ratio H/G.

Entry	$\frac{[H]t}{([H]_t+[G]_t)}$	A_{obs} at 468 nm (Au)
1	0.00	0.0000
2	0.10	0.0232
3	0.20	0.0344
4	0.30	0.0456
5	0.40	0.0658
6	0.50	0.0510
7	0.60	0.0462
8	0.70	0.0384
9	0.80	0.0456
10	0.90	0.0178
11	1.00	0.0000

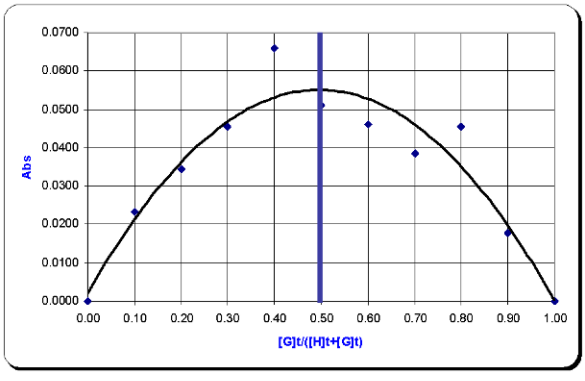


Figure 1. Modified Job's Plot for complexation of H7 with TBAA by UV-Vis spectroscopy.

at 348 nm diminishing, while another band at 468 nm was appearing, upon addition of TBAA. The 468 nm band was attributed to the orange complex H7-TBAA. Another amino-thiourea which underwent complexation is H9 gave a shift in absorption band from 280 nm to 314 nm. For the guanidine H12 and its hydrochloride H13 we obtained the same bathochromic effect (354→375 nm). The presence of hydrochloric acid has no influence in this complexation.

It was interesting to observe that the *bis*-thioureas H1-3 and *bis*-urea H4 did not undergo complexation. In the amino series of thioureas H5-H10 and urea H11, the complexation occurred only for compounds H7 and H9. Electronic effects can indeed offer an explanation, since compounds H7 and H9 contain a strong electron withdrawing group (-NO_2 and –CF_3, respectively), which increases the acidity of the –NH– group vicinal to the aryl group.

The resulting complexes (Table 2) are moisture sensitive and special precautions have to be taken.

The most stable complex proved to be the H7-TBAA complex. In this case, we could calculate the association constant.

The review by Hirose [23] and the paper by Hargrove [24] are very useful resources for the calculation of binding constants. The steps involved in this process are: a) determination of the stoichiometry; b) evaluation of the complex concentration [C]; c) setting up the concentration conditions for the host and guest, d) data treatment. The stoichiometry was determined using the *Continous Variation Method*, the following four steps being observed: 1) keeping the sum of $[H]_t$ and $[G]_t$ constant (α); 2) variation of $[H]_t$ from 0 to α; measuring the concentration of the complex, [C] and 4) data treatment (Job's Plot – complex formation *vs.* host/guest ratio).

According to the Lambert-Beer law, the absorbance is the product of the extinction coefficient and the molar concentration of the studied compound: $A_C = \varepsilon_C \cdot [C]$, where A_C is the absorbance and ε_C is the molar extinctions of the complex.

In our case, since neither the host nor the guest are showing any absorption bands at 468 nm, this value can be attributed to the sole complex and the concentration of the complex becames $[C] = A_{obs}/\varepsilon_C$.

By measuring the absorbance of the complex at ratios H/G varying from 1:0 to 0:1, at constant sum of concentrations (Table 2), a modified Job's plot can be created (Fig. 1).

The stoichiometry of the complexation is determined on the *x* ordonate at the maximum of the curve and in our case is at $x = 0.5$ corresponding to a 1:1 stoichiometry. The concentration of the complex can be calculated using the equation $[C] = A_{obs}/\varepsilon_C$. Since the molar absorption of the complex (ε_C) cannot be measured directly, a titration experiment and a regression are needed. The titration experiment (Fig. 2) consists in a progressive increase of

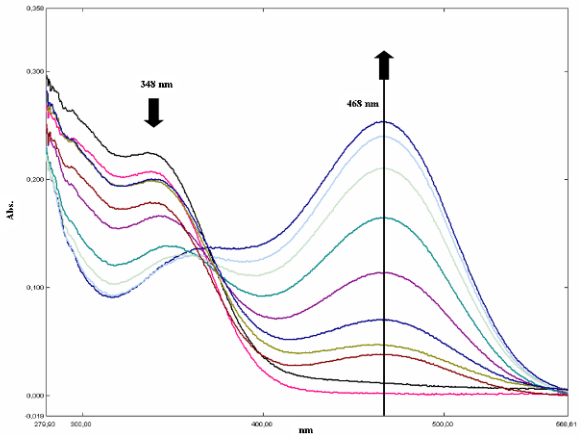


Figure 2. Absorption spectra of H7 (2×10^{-5} M) in the presence of increasing amounts of TBAA (4×10^{-6} → 1.2×10^{-3} M, 0.2 → 60 eq) in acetonitrile.

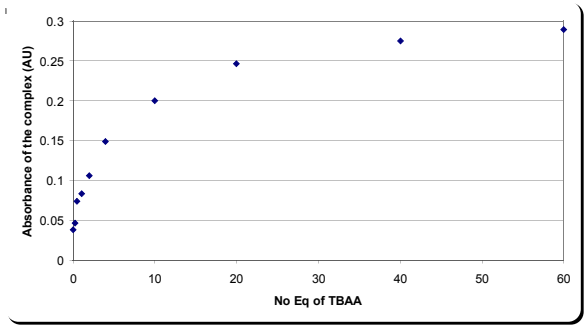


Figure 3. Titration of H7 with TBAA in acetonitrile.

Table 4. Titration of H7 with TBAA in acetonitrile.

Entry	No. eq. of guest	A_{obs} (AU)
1	0	0.000
2	0.2	0.009
3	0.5	0.036
4	1	0.045
5	2	0.068
6	4	0.111
7	10	0.162
8	20	0.208
9	40	0.237
10	60	0.251

the guest/host ratio until the maximum of absorbance is reached. In our case it was observed at 60 equivalents of TBAA.

At the maximum of absorbance the concentration of the complex is approximately equal to the concentration of the host, $[C] = [H]_t = 2\times10^{-5}$ M. Thus, the molar extinction coefficient of the complex is calculated as $\varepsilon_C = 14500$ L mol^{-1} cm^{-1}. The value of the association constant is obtained by linear regression minimizing $\Sigma(A_{calc}-A_{obs})^2$ for all A_{obs}. From the initial concentration of the guest, it is possible to calculate the concentration of the complex and from its value the absorbance A_{calc}. Knowing the extinction coefficient and [C], the minimum condition is reached for K = 7500 mol^{-1} L^{-1}. Comparison with other association constants reported for thiourea and tetra-*n*-butylammonium acetate (ca 10^5-10^6 mol^{-1} L^{-1}) [25,26] reveals that the association constant we observed is small.

The complexation capacity of the tested ureas, thioureas and guanidines can be explained by their conformation and by the proton availability in these compounds. The *bis*-derivatives (H1-H4) and amino-derivatives (H5-H11) have totally different conformational states.

The X-ray structure of *bis*-thiourea H2 (Fig. 4a) offers important informations about the conformation of this compound in solid state. The two NH of the thiourea have an *anti* orientation, which is not favourable for efficient carboxylate recognition. It is also noticeable that one of the NH necessary for the complexation is already involved in an intramolecular NH···O hydrogen bond. This bond is created between the NH protons neighboring the aliphatic moiety and the oxygen atoms from the dioxolane ring. The hydrogen bonds stabilize the molecule by changing the conformation from "current" to "un-current" [15] and thus the acetate approach is highly unlikely, due to steric hindrance. The same pattern can be observed for the other *bis*-thioureas (H1-H3). The occurrence of an intramolecular hydrogen bond for one NH and the steric hindrance of the other NH account for the lack of complexation of the carboxylate anion by *bis*-(thiourea) H1-H4.

Aminothioureas (H5-H11) have a very different conformational orientation compared to their *bis*-substituted analogues. A strong intramolecular NH···NH_2 hydrogen bond, 2.111 Å in length, can be observed in the X-ray of H7 (Fig. 4b). This bond is formed between the hydrogen from the NH group bearing the chiral moiety of the thiourea and the nitrogen of the NH_2 group.

This hydrogen bond is probably strong and prevents any complexation of the carboxylate anion by the NH involved in such an intramolecular H-bonding. The *anti* conformation of the thiourea is not favorable for double hydrogen bonding however the hydrogen of the second NH bearing the aryl group is accessible to carboxylate anion and its acidity is tuned by the substituents on the aryl. In the lattice of H7 we observed two molecules of acetone; one of them being involved in a hydrogen bond with the NH_2. This supplementary intermolecular hydrogen bonding is possibly due to the acidification of the two protons from the amino group by the intramolecular hydrogen bond. In summary, the observed complexation capacity of the two aminothioureas (H7 and H9) rests on

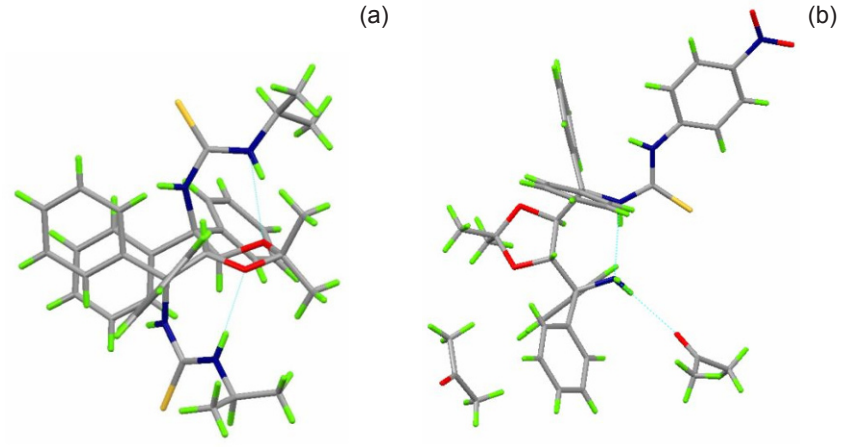


Figure 4. X-Ray structures of the (*S,S*) bis-thiourea H2 (left - 4a) and (*S,S*) amino-thiourea H7 (right – 4b) obtained from (*R,R*) TADDOL.

the sole availability and the acidity of the hydrogen of the NH bearing the aryl moiety of the thiourea group.

The occurrence of the intramolecular N-H···NH_2 hydrogen bond in aminothiourea H7 was also observed in solution by ^{1}H NMR spectroscopy: the singlet that appears at 12.71 ppm in $CDCl_3$ can be assigned to a hydrogen atom involved in a strong hydrogen bond. The signal belongs to the closest –NH- group to the TADDAMINE moiety. The chemical shift for the NH group involved in the hydrogen bond ranges from 11.93 ppm for H5 to 12.71 ppm for H7. The chemical shift of the proton of the second NH is highly sensitive to the nitrogen substituent. It ranges from 4.90 ppm for the methyl substituted one to 6.92 ppm for the 4-NO_2-C_6H_4- one monitoring the acidity of the protons attached to the nitrogen atoms.

4. Conclusions

We created a focused library of new chiral enantiopure *bis*-thioureas, *bis*-ureas, amino-thioureas, amino-ureas and guanidines with (*S,S*) configuration derived from (*R,R*)-TADDOL. These compounds were obtained by simple methods from TADDOL derivatives, such as isothiocyanates, isocyanates, and TADDAMINE, in high yields.

Their complexation capacity toward carboxylate recognition was tested using tetra-*n*-butylammonium acetate as a guest. Four compounds, namely the two aminothioureas (H7 and H9), one guanidine (H12) and its hydrochloric salt (H13), complex with TBAA in acetonitrile. This process was investigated by UV-Vis spectroscopy and for one of the aminothioureas (H7) the association constant was determined as K = 7500 mol^{-1} L^{-1}. The weak complexation capacity was explained by electronic and conformational factors.

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