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## HOST-GUEST CHEMISTRY OF TOLBUTAMIDE

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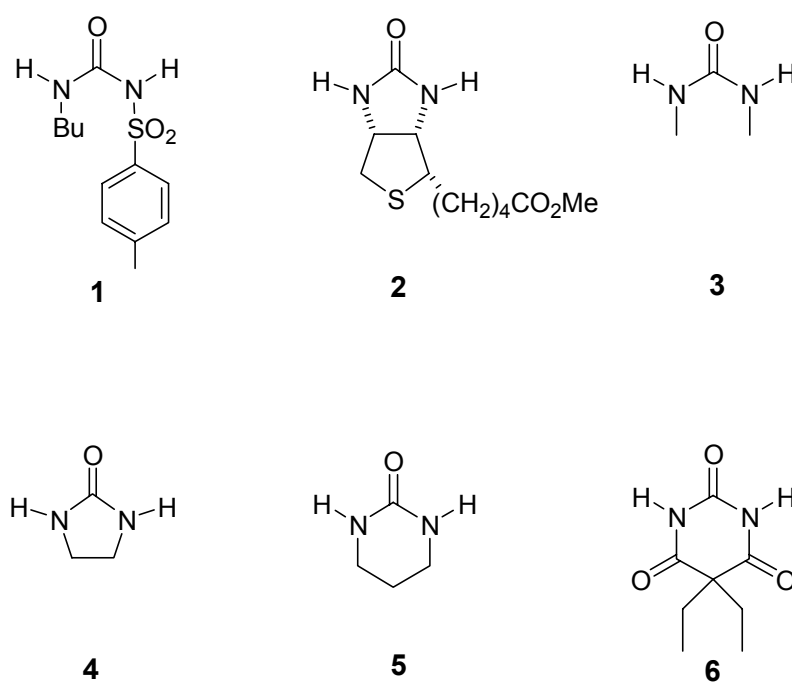
### **Abstract**

*The molecular recognition features of tolbutamide with four synthetic hosts have been studied by means of NMR titrations, NOESY experiment and Monte Carlo (MC) conformational search. The interaction strength and the most probable structure reveal new insights on the recognition phenomena of this urea derivative in comparison with close related compounds.*

### **Introduction**

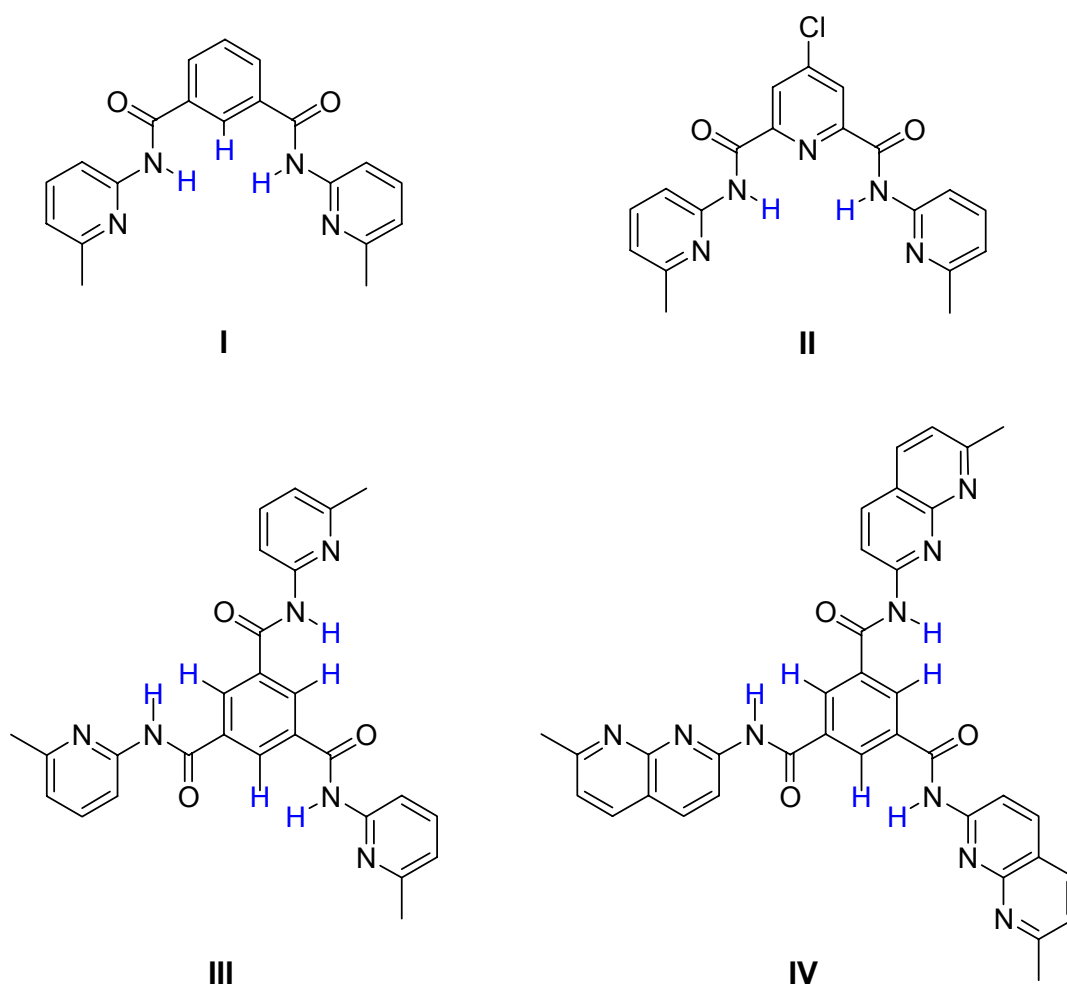
In preceding papers we have carried out the systematic study of host-guest complexes using urea and biotin related compounds of biological interest as guests, with the final purpose to mimic the function of natural receptors by means of an iterative optimisation approach.<sup>[1,2]</sup> Here we have applied the same methodology to a new guest, the anti-diabetic oral hypoglycaemic agent tolbutamide (**1**), this compound is a sulfonyl urea related to our previous guests

(biotin methyl ester (**2**), *N,N'*-dimethylurea (**3**), 2-imidazolidone (**4**), *N,N'*-trimethylenurea (**5**) and barbital (**6**)) but with a sulfonyl group that can change its properties (Figure 1).



**Figure 1.** Structure of tolbutamide (**1**) and related guests

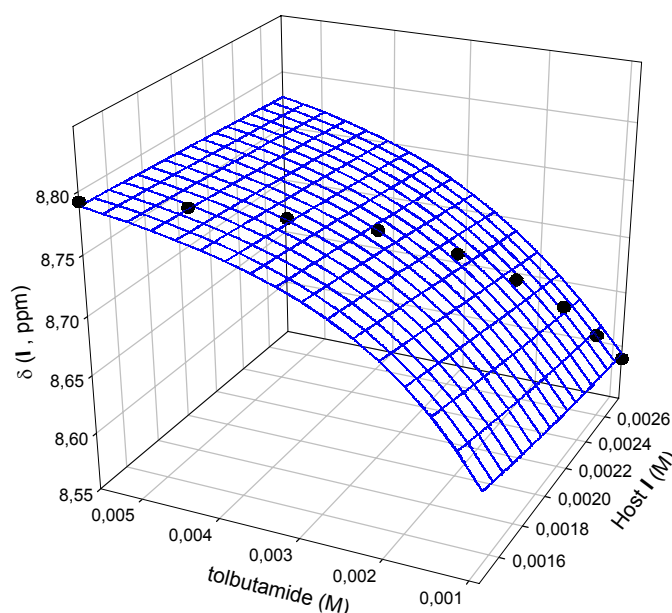
We have studied the complexes established between tolbutamide and four synthetic hosts (Figure 2) *N,N'*-bis(6-methylpyridin-2-yl)-1,3-benzenedicarboxamide (**I**), 4-chloro-*N,N'*-bis(6-methylpyridin-2-yl)-2,6-pyridinedicarboxamide (**II**), *N,N',N''*-tris-(6-methylpyridin-2-yl)-1,3,5-benzenetricarboxamide (**III**) and *N,N',N''*-tris-(7-methyl-1,8-naphthyridin-2-yl)-1,3,5-benzenetricarboxamide (**IV**).



**Figure 2.** Structures of hosts I-IV

$^1\text{H}$  NMR titrations have been performed to measure the binding constants ( $K_b$ ) of hosts **I**, **III** and **IV** with tolbutamide by a direct method, using the Chemical Induced Shifts (CIS) on the 2-CH benzenic proton and the NHs of the 1,3-dicarboxamide groups (blue protons in Figure 2). Due to the interaction between host **II** and water the competitive titration method was needed to determine  $K_b$  value, measuring the NH-CIS of the urea moiety in tolbutamide and the  $\text{H}_2\text{O}$ -CIS.<sup>[2-5]</sup>

As we have previously proved a careful determination of the best concentrations of host and guest must be carried out if the aim is the measurement of meaningful binding constants with the lowest error. All the titrations have been performed in such a way that the saturation fractions of both host and guest are between 20%-80%, avoiding situations where the chemical induced shifts, of the monitored protons, is zero. In these conditions a soft titration curve, with no linear behavior is obtained and the data are non-linear fitted by the use of Sigmaplot software obtaining curves like the one shown in Figure 3.



**Figure 3.** Titration curve for the complex 1:1

All complexes have been modelled using Monte Carlo conformational search with AMBER force field (MacroModel v.8.1).<sup>6</sup> This procedure affords the most probable structure of the complex and allows us to get useful information about the binding mode of the guest.

## Results and discussion

### *Binding constants*

The experimental binding constants  $K_b$  measured in  $CDCl_3$  at 300 K for complexes of hosts **I-IV** with tolbutamide (**1**) are gathered in Table 1, together with the values previously measured by us with the other guests (**2-6**), introduced for comparative purposes.

**Table 1.** Experimental binding constants  $K_b$  ( $M^{-1}$ )

	<b>I</b>	<b>II</b>	<b>III</b>	<b>IV<sup>a</sup></b>
<b>tolbutamide (1)</b>	<b>600</b>	<b>735</b>	<b>900</b>	<b>820</b>
<b>2</b>	975	3600	4000	148000
<b>3</b>	$\leq 10$	$\leq 10$	34	-
<b>4</b>	1450	140	4800	33000
<b>5</b>	2300	100	5700	21000
<b>6</b>	2375	275	6100 <sup>b</sup>	-

<sup>a</sup> The  $K_b$  values with guests **3** and **6** were not determined due to the lack of solubility of the complexes.

<sup>b</sup> This complex shows a 2:1 stoichiometry with a second  $K_b$  equal to  $1400 M^{-1}$

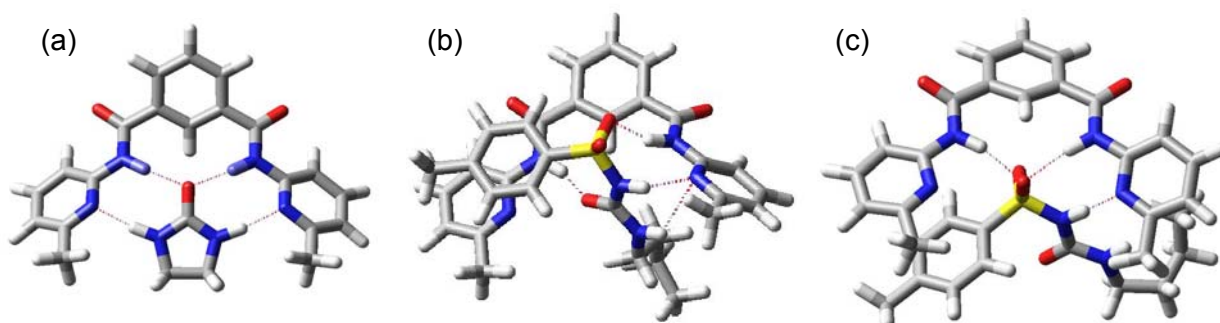
Tolbutamide forms complexes of similar stabilities with all hosts, even the great difference in the structure of these compounds. Guests like biotin methyl ester (**2**) establish a weak interaction with **I** but a quite strong one with **IV**, in fact the obtained complex is the strongest one ever found between a biotin analog and a synthetic receptor.

Another difference of tolbutamide is the behavior of the signals, of both the hosts and the guest, in the  $^1H$ -NMR spectra. With the other guests **2-6** the  $K_b$  determination is carried out following the chemical induced shift of the protons indicated in blue in Figure 2. So for hosts **I**, **III** and **IV** two different

protons can be used, the benzenic and the amide protons. However, in the titrations of tolbutamide there was no variation on the signals of the benzenic protons indicating an interaction through a different binding mode. On the other hand for tolbutamide, during the titration, the shift in the signals was only observed for the NH proton close to the sulfonyl group while the other NH proton remained unchanged. To explain this different behavior we use the information provided by the modelling of these complexes.

#### *Molecular modelling. Structure of the complexes*

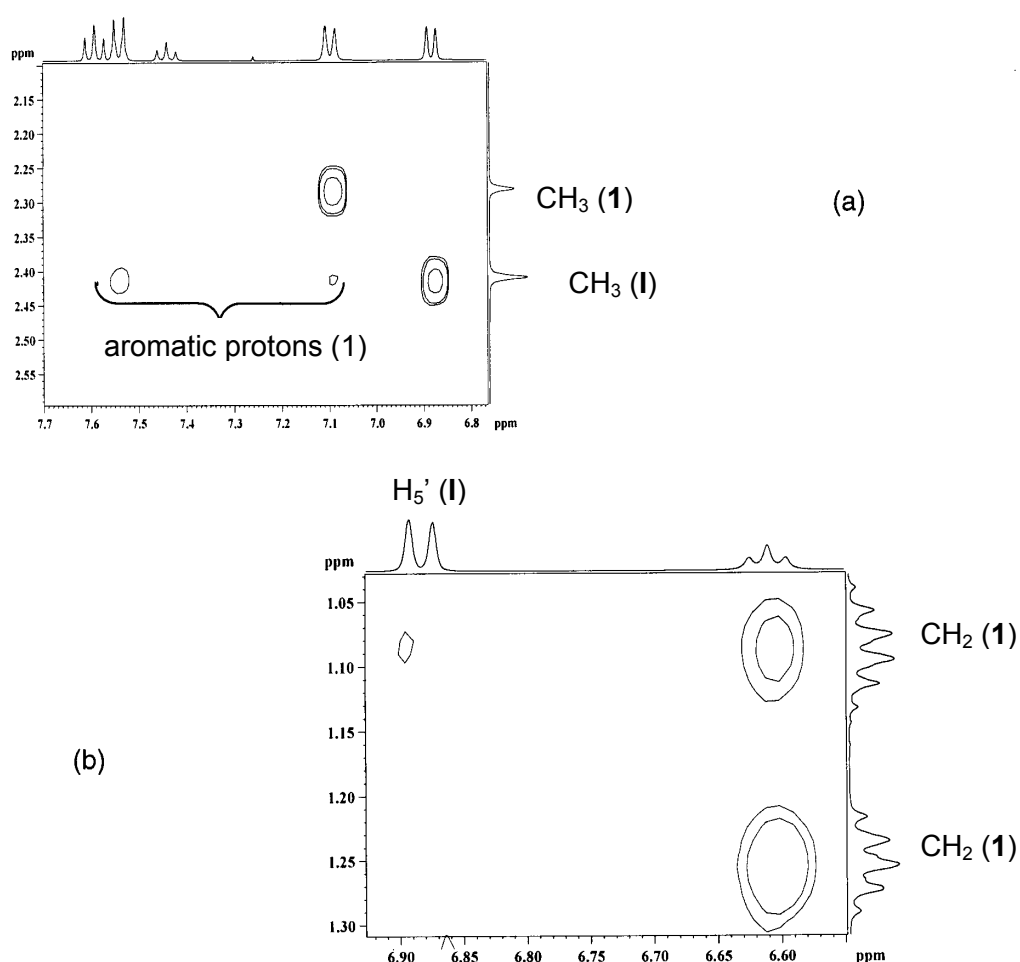
In Figure 4 three minimized structures, found in the MC search, are shown. The structure shown in Figure 4a belongs to the complex between host **I** and 2-imidazolidone (**4**) and it is the usual way of binding for this kind of compounds through the urea moiety.



**Figure 4.** Minimum energy structure for complexes **I:4** (a), **I:1** (b) and **I:1**(NOESY) (c)

Modelling of complex **I:1** afforded the structure shown in Figure 4b ( $-73.4 \text{ kJ mol}^{-1}$ ), but this structure does not fit experimental data obtained during NMR titration where only the chemical shift of NH signal next to sulfonyl group changes, indicating that the other NH close to butyl substituent is not interacting with the host. Trying to get some information about the relative position of *p*-tolyl and butyl substituents we carried out a NOESY experiment (Figure 5). On this

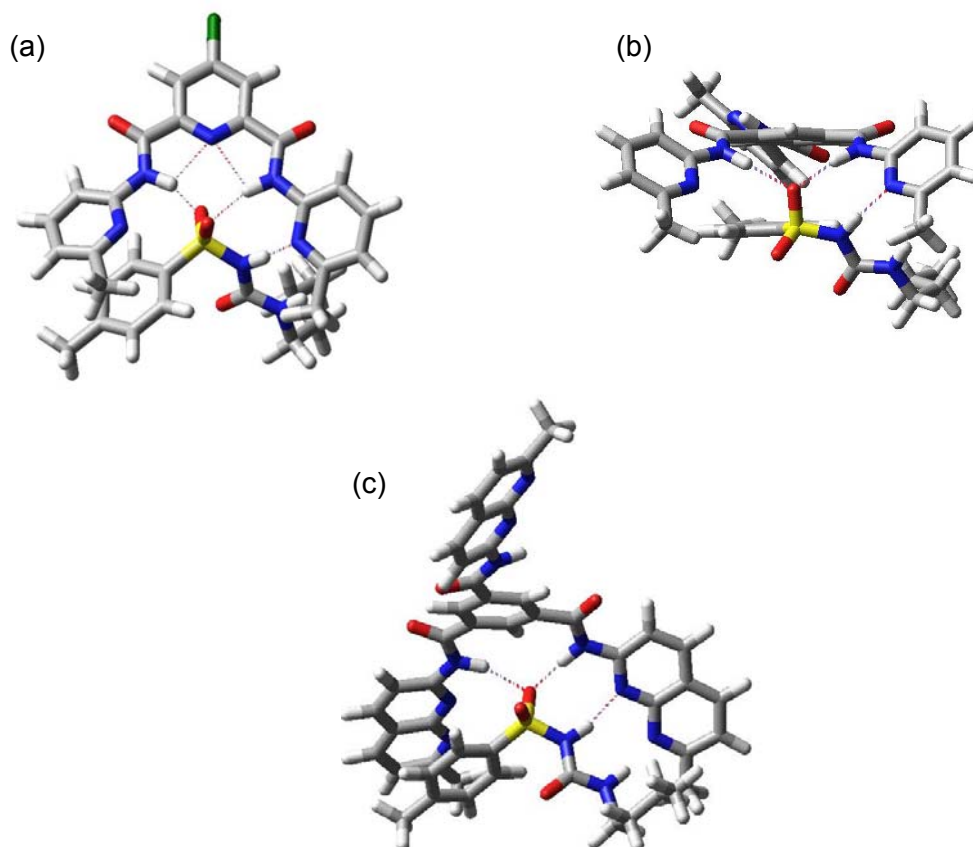
way we observed weak cross peaks indicating the closeness of the *p*-tolyl protons of tolbutamide (**1**) to the methyl group of host **I** (Figure 5a) and the guest butyl protons to host pyridine ones (Figure 5b). Introducing this information in a new MC search we obtained the structure shown in Figure 4c (-63.4 kJ mol<sup>-1</sup>), where the hydrogen bonds are formed between the sulfonyl group of the guest and NH amides of the host, and between the NH bonded to the sulfonyl and N in pyridine, in agreement with experimental data.



**Figure 5.** Enlarged regions of the NMR NOESY spectrum for complex **I**:**1**

The minimum energy structure for complexes of tolbutamide (**1**) with hosts **II**, **III** and **IV** are shown in Figure 6. In all cases the binding mode is the

same that we found in the complex with host **I** in agreement with the experimental data.



**Figure 6.** Minimum energy structure for complexes **II:1** (a), **III:1** (b) and **IV:1** (c)

From these data it is clear that tolbutamide (**1**) is rather different from the other studied ureas because the sulfonyl group not only increases considerably the acidity of the contiguous NH but also modifies the conformation in the complex. In all cases the most stable conformation for tolbutamide is the *Z,Z* with the NH protons opposite to urea carbonyl unlike guests **2** to **6**. The effect of the sulfonyl compensates the small  $K_b$  value that could be expected due to the rotational isomers of this molecule.<sup>2</sup>



## Conclusions

The binding mode of tolbutamide is driven for the presence of the sulfonyl group, because of that this guest shows a host-guest chemistry totally different from other ureas where the interaction takes place through the urea moiety.

We have proved how the use of NMR titrations and molecular modelling allow to reach a deeper understanding on the molecular recognition features of urea derivatives.

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## Acknowledgements

An FPI fellowship to one of us (F H R) and economic support from the McyT of Spain (project number BQU2003-00976) is greatly acknowledged.