MOLECULAR MODELING: PREDICTION OF THE STRUCTURE OF HOST-GUEST COMPLEXES

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Abstract

The molecular recognition features of urea derivatives including (+)-biotin methyl ester with hosts containing 2,6-bisamidopyridine or 2,5-bisamidopyrrole bearing pyridyl or 1,8-naphthyridyl groups have been studied by Monte Carlo (MC) conformational search. The most probable conformation and the associated energy of the complexes have been obtained.

Keywords: Molecular Recognition; Monte Carlo conformational search; Pyridines; Pyrroles

Introduction

Molecular modeling has become a standard method for predicting binding properties in supramolecular chemistry for several reasons. First of all, the geometric fit between several molecules, which is at the core of host-guest phenomena, can be easily controlled by these techniques. In contrast to molecular orbital methods, molecular mechanics force fields (MM) have the advantage of giving a direct picture of the interacting groups; they provide a better and practical lead for the chemist to understand and to design supramolecular complexes.

This communication reports the most stable conformations for 1:1 host-guest complexes between four guests containing the urea motif: (+)-biotin methyl ester (**1**), 2-imidazolidone (**2**), *N*,*N*'-trimethylenurea (**3**) and barbital (**4**) with the synthetic receptors **5**-**8**, all of them depicted in Figure 1, obtained by using of Monte Carlo conformational search with the AMBER force field. The main driving forces for complexation between the host and the guest will be analyzed.

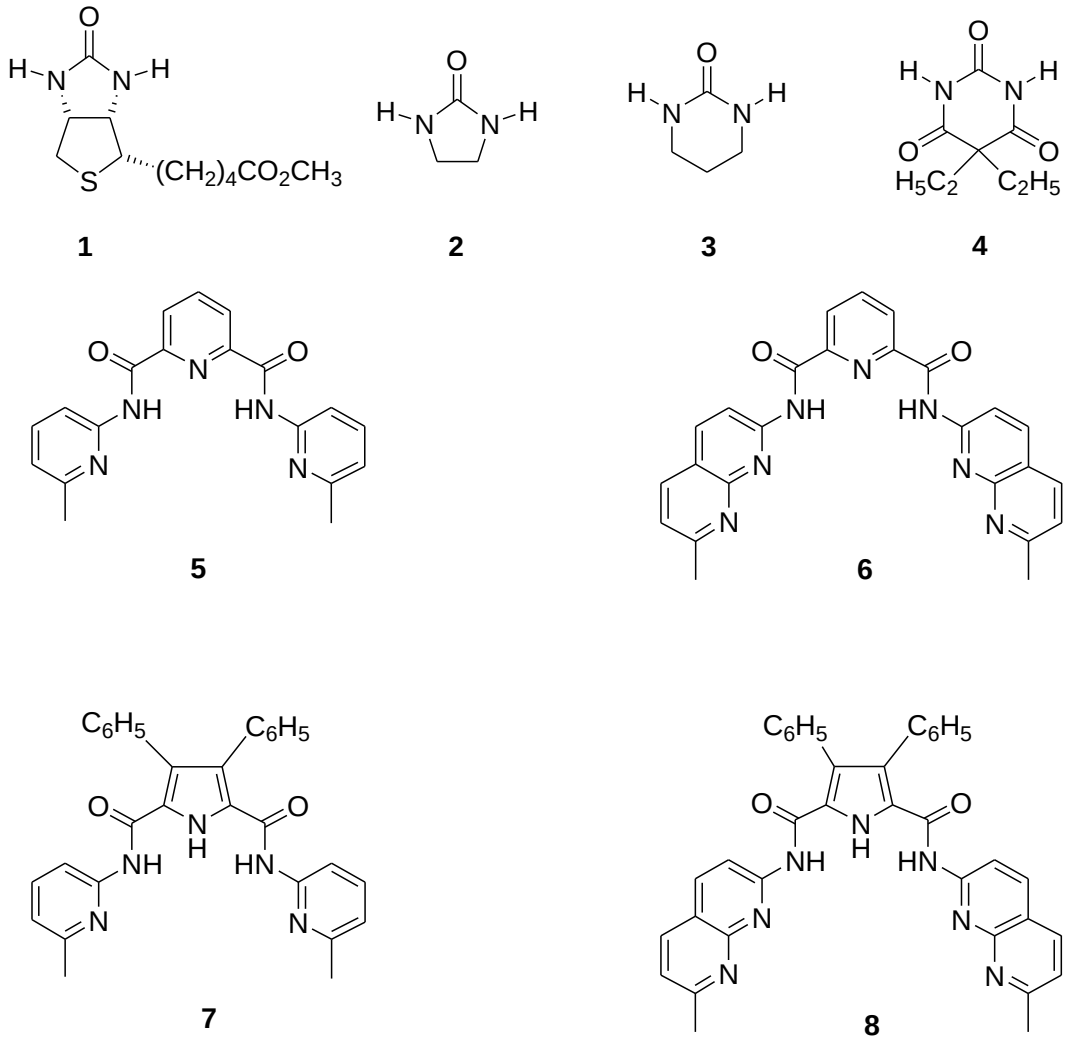

Figure 1. Studied guests (**1**-**4**) and hosts (**5**-**8**).

This work has been developed on the frame of our project aimed at optimizing the interactions between hosts and guests following an iterative approach, alternatively optimizing the host and the guest. The final purpose is to attain association constants that would approach asymptotically that of the complex biotin/avidin (or streptavidin).[1-6]

Results and discussion

All complexes have been modelled using Monte Carlo conformational search with the AMBER force field (MacroModel v.8.1, see Experimental Procedure). This procedure affords the most probable structure of the complex and allows us to get useful information about the binding mode of the guest. The structure of the complexes is created from minimum energy conformations of hosts and guests, obtained from Monte Carlo conformational searches. The interaction energy for complex is obtained using equation (1).

$$E_{interaction} = E_{min.}\ (Complex) - E_{min.}\ (Host) - E_{min.}\ (Guest) \qquad (1)$$

Minimum energy values for complexes are gathered in Table 1 and the most stable conformations for hosts **5**-**8** are shown in Figure 2.

Tabla 1. Interaction energy values $-E_{min}$ (kJ mol^{-1}) for the complexes of hosts **5**-**8** with guests **1**-**4**.

	5	**6**	**7**	**8**
Methyl biotin (**1**)	68.0	70.5	64.8	72.0
2-imidazolidone (**2**)	51.7	57.5	43.7	52.1
N,*N*′-trimethyleneurea (**3**)	57.7	59.5	46.2	54.8
barbital (**4**)	74.8	108.5	59.1	90.9

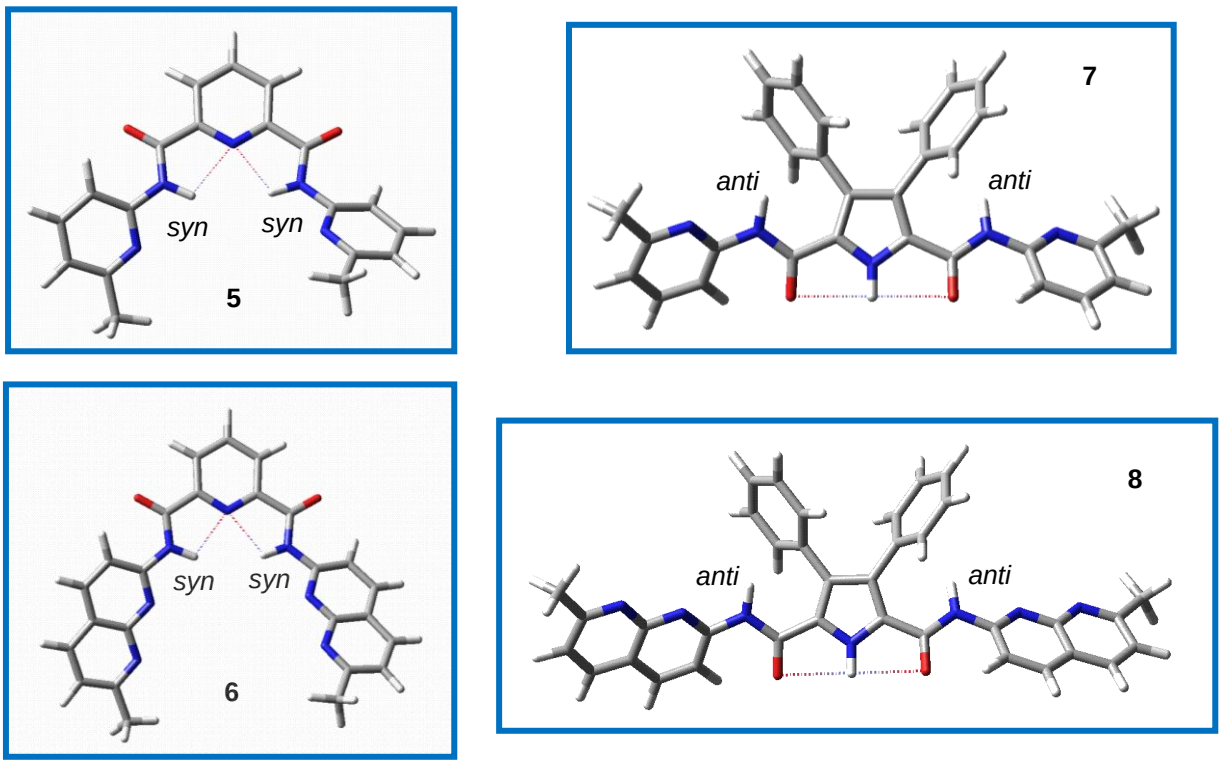

Figure 2. Minimum energy conformations of hosts **5**-**8**.

In Figure 2 we can see the differences in the most stable conformation between the receptors derived from pyridine **5**-**6** and pyrrole **7**-**8**. In all cases the formation of two intramolecular hydrogen bonds is responsible for the most stable conformation. Hosts **5**-**6** show a *syn*, *syn* conformation that allows the preorganization of the two amide NH atoms inwards for optimal guest binding. However, in hosts **7**-**8** the formation of two intramolecular hydrogen bonds between the NH pyrrole and amide CO groups determine the preferred *anti*, *anti* conformation.

In Figure 3 the minimum energy structure for some complexes is shown. We can observe that the interaction mode for the complexes with (+)-biotin methyl ester (**1**), 2-

imidazolidone (**2**) and *N*,*N*'-trimethylenurea (**3**) is much alike and in accordance with the usual binding mode for this kind of compounds - through the urea moiety. However, that of barbital (**4**) uses only the carbonyl group.

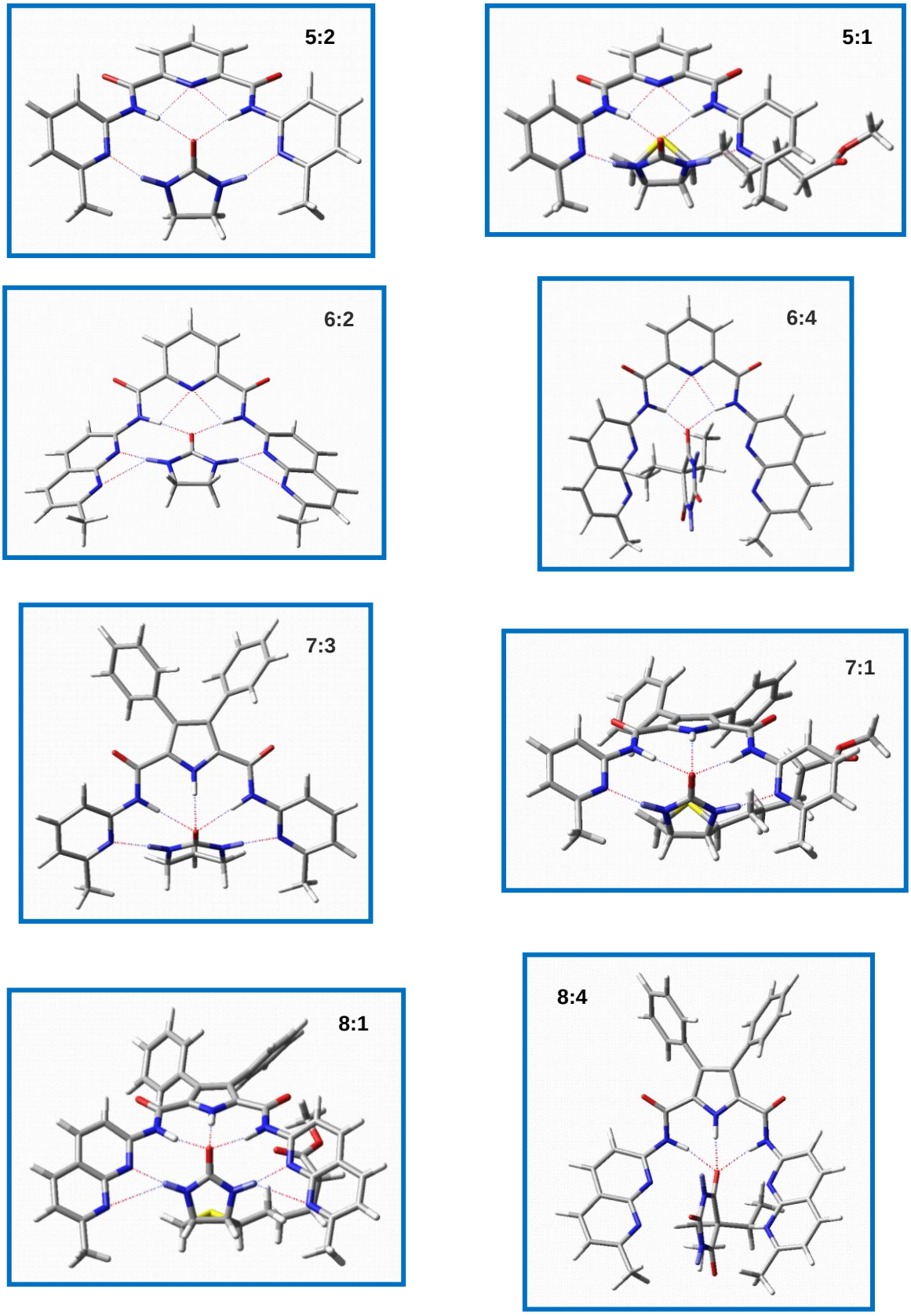

Figure 3. Minimum energy conformations of some complexes.

Hosts **6** and **8,** bearing naphthyridine units, give rise to more stable complexes than those formed by hosts **5** and **7**, containing pyridine units, due to the extra hydrogen bonds between the NH urea groups and the N8' naphthyridine nitrogens.

On the other hand, in the complexes formed by hosts **7** and **8** the additional hydrogen bond arising from the pyrrolic NH compensates energetically the necessary conformational change in receptor to bind guests.

Parameters for selected hydrogen bonding interations related to hosts-guests binding are collected in Table 2.

Table 2. A comparison of DH···A hydrogen bonding in Hosts (**H**)- Guests (**G**) complexes according to the numbering system given in Figure 4.

	5		**6**		**7**		**8**	
	d (Å)	**α (°)**	**d (Å)**	**α (°)**	**d (Å)**	**α (°)**	**d (Å)**	**α (°)**
(+)-Methyl biotin ester (**1**)								
NH1(**H**)···CO(**G**)	1.889	166.1	1.851	165.3	2.001	177.0	1.985	164.4
NH2(**H**)···CO(**G**)	1.887	167.5	1.852	159.6	1.981	171.5	2.019	165.0
NH1(**G**)···N1'(**H**)	1.973	158.8	1.921	152.8	1.961	171.7	1.895	168.9
NH3(**G**)···N1'(**H**)	1.960	159.1	1.926	159.7	1.939	172.6	1.911	171.6
NH1(**G**)···N8'(**H**)			2.392	136.9			3.013	139.6
NH3(**G**)···N8'(**H**)			2.624	141.7			2.982	139.2
NH3(**H**)···CO(**G**)					1.881	140.4	1.743	166.7
2-Imidazolidone (**2**)								
NH1(**H**)···CO(**G**)	1.833	168.0	1.874	168.5	1.946	176.4	1.938	178.4
NH2(**H**)···CO(**G**)	1.822	169.7	1.856	170.1	1.952	169.3	1.934	173.5
NH1(**G**)···N1'(**H**)	1.948	159.6	1.925	155.6	1.999	169.5	1.935	163.3
NH3(**G**)···N1'(**H**)	1.947	160.3	1.922	156.1	1.941	171.1	1.932	164.8
NH1(**G**)···N8'(**H**)			2.438	136.5			2.571	138.4
NH3(**G**)···N8'(**H**)			2.470	136.4			2.617	138.0
NH3(**H**)···CO(**G**)					1.726	161.6	1.714	168.2
N,N'-Trimethylenurea (**3**)								
NH1(**H**)···CO(**G**)	1.840	167.4	1.875	169.3	1.952	172.1	1.956	179.0
NH2(**H**)···CO(**G**)	1.828	168.6	1.859	170.5	1.951	179.3	1.943	172.8
NH1(**G**)···N1'(**H**)	1.929	168.1	1.898	162.6	1.926	176.8	1.907	177.6
NH3(**G**)···N1'(**H**)	1.930	168.9	1.897	163.0	1.923	177.7	1.908	178.7
NH1(**G**)···N8'(**H**)			2.669	124.8				
NH3(**G**)···N8'(**H**)			2.689	124.9				
NH3(**H**)···CO(**G**)					1.736	159.9	1.723	164.8
Barbital (**4**)								
NH1(**H**)···CO(**G**)	1.737	160.4	1.780	159.6	1.831	170.9	1.898	160.6
NH2(**H**)···CO(**G**)	1.747	159.6	1.805	157.9	1.816	172.2	1.914	160.9
NH3(**H**)···CO(**G**)					1.672	167.7	1.693	167.2

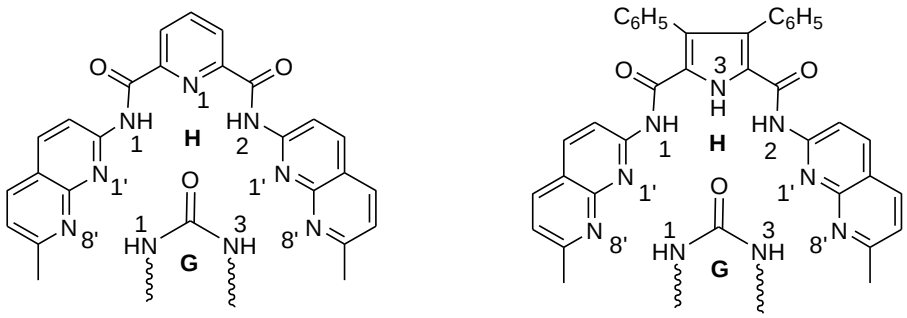

Figure 4. Numbering system used for DH···A hydrogen bonding in Table 2.

Experimental Procedure

MacroModel v.8.1, with the GB/SA model for chloroform was used to perform the molecular simulations of the complexes [7]. All calculations were achieved with Montecarlo (MC) conformational analyses. Minimisation is carried out using Polak-Ribiere Conjugate Gradient (PRCG) method as implemented in the program version, the energy gradient was chosen as the convergence criteria with a value of 0.05, and at least 2000 iterations. All MC calculations were performed with MCMM (Monte Carlo Multiple Minimum) method, and the variables were torsion angles, molecule coordinates or both. The minimization method was PRCG with the same characteristics decribed above. In a typical MC run a MCMM is never performed with less than 8000 steps, to carry out the search both torsional rotations in host and guest and translation/rotation (10 Å/360º) of the guest is performed, for all the MC a cutoff is applied to van der Waals, electrostatic and H-bond interactions with 7, 12 and 4 Å respectively. These calculations were carried out with the AMBER* force field as implemented in the version of the program.

Acknowledgments

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References

[1] R. M. Claramunt, F. Herranz, M. D. Santa María, C. Jaime, M. de Federico, J. Elguero, Towards the design of host-guest complexes: Biotin and urea derivatives *versus* artificial receptors, *Biosens. Bioelectron.* **2004**, *20*, 1242-1249.

[2] R. M. Claramunt, F. Herranz, M. D. Santa María, E. Pinilla, M. R. Torres, J. Elguero, Molecular recognition of biotin, barbital and tolbutamide with new synthetic receptors, *Tetrahedron* **2005**, *61*, 5089-5100.

[3] F. Herranz, M. D. Santa María, R. M. Claramunt, Molecular Recognition: Improved binding of Biotin Derivatives with Synthetic Receptors, *J. Org. Chem*. **2006**, *71*, 2944-2951.

[4] F. Herranz, M. D. Santa María, R. M. Claramunt, Host-Guest Chemistry of Tolbutamide, *Molecules* **2006**, *11*, 478-485.

[5] F. Herranz, M. D. Santa María, R. M. Claramunt, A new tool for the rational design of methylbiotin host, *Tetrahedron Lett.* **2006**, *47*, 9017-9020.

[6] J. C. Iglesias, D. Santa María, R. M. Claramunt, J. Elguero, Molecular Recognition Studies on Naphthyridine Derivatives, *Molecules* **2010**, *15*, 1213-1222.

[7] MacroModel, Schrödinger LLC, 2004. http://www.schrodinger.com