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Weak C–H/π Interaction Participates in the Diastereoselectivity of a Host–Guest Complex in the Presence of Six Strong Hydrogen Bonds

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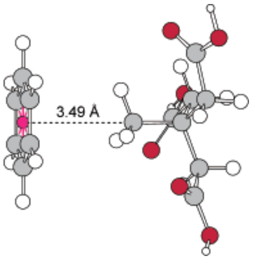
ABSTRACT



We report a study of the interaction between methylmethanetriacetic acid (MMTA) and a tripodal amidopyridine receptor 1, where the geometry of the binding is in part governed by a weak C–H/π interaction in the presence of six strong N(O)–H···O(N) hydrogen bonds. There are two possible binding geometries for the 1:1 complex 1·MMTA; combining computational and experimental evidence we demonstrate that the *endo* binding mode is more favorable as the result of a C–H/π interaction.

The C–H/π interaction[1] can be defined as the attraction between the C–H bond and the π system[2] and has recently gained attention in the consideration of a variety of molecular phenomena. Despite being the weakest among the hydrogen bonds, it has been found in a variety of substances to play important roles in their physical, chemical, and biological properties.[3–6] Whereas the enthalpy for a "conventional hydrogen bonds" is within the range of 3–7 kcal/mol, the one for a one-pair C–H/π interaction is presumed to be less than 1 kcal/mol.[7] The total energy of the interaction is increased by organizing CHs or π-groups into favorable structures. This point is important in understanding the role of weak interactions. Hunter's group[8] has used an amide macrocycle with a highly preorganized cavity containing both polar and nonpolar recognition sites to form stable complexes with cyclic peptides in water via hydrogen–bonds, N–H/π, and C–H/π interactions.

Some of us have previously reported[9] a synthetic methodology for preparing 1,3,5-triaryl-substituted benzenes in multigram quantities. In this letter, we report a study of the interaction between methylmethanetriacetic acid (MMTA) and a tripodal amidopyridine receptor **1**, where the geometry

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(1) Kodama, Y.; Nishihata, K.; Nishio, M.; Nakagawa, N. *Tetrahedron Lett.* **1977**, *18*, 2105.

(2) Nishio, M.; Hirota, M.; Umezawa, Y. The C–H/π Interaction. *Evidence, Nature, and Consequences*; Wiley-VCH, Inc.: New York, 1998.

(3) Quiocho, F. A.; Vyas, N. K. *Nature* **1984**, *310*, 381.

(4) Vyas, N. K.; Vyas, M. N.; Quiocho, F. A. *Nature* **1987**, *327*, 635.

(5) Umezawa, Y.; Tsuboyama, S.; Takahashi, H.; Uzawa, J.; Nishio, M. *Tetrahedron* **1999**, *55*, 10047.

(6) Amabilino, D. B.; Ashton, P. R.; Balzani, V.; Boyd, S. E.; Credi, A.; Lee, J. Y.; Menzer, S.; Stoddart, J. F.; Venturi, M.; Williams, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 4295.

(7) Tsuzuki, S.; Honda, K.; Uchimaru, T.; Mikami, M.; Tanabe, K. *J. Am. Chem. Soc.* **2000**, *122*, 3746.

(8) Allot, C.; Bernard, P. L.; Hunter, C. A.; Rotger, C.; Thomas, J. A. *Chemm. Commun.* **1998**, 2449.

(9) Rotger, M. C.; Costa, A.; Saá, J. M. *J. Org. Chem.* **1993**, *58*, 4083.

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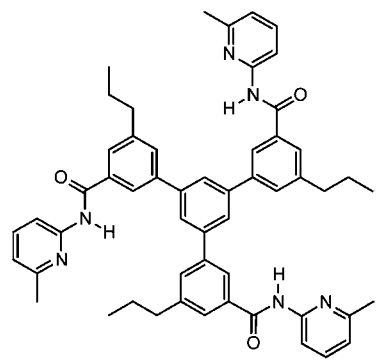

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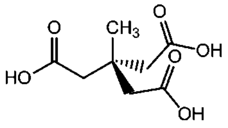

MMTA

of the binding is in part governed by a weak $C-H/\pi$ interaction in the presence of six strong N(O)−H···O(N) hydrogen bonds. There are two possible binding geometries for the 1:1 complex **1**·MMTA, depending on the orientation of the methyl group with respect to the receptor cavity. Apparently, the *exo* geometry ((**1**·MMTA)$_b$, Figure 1) is expected to be more favorable than the *endo* (**1**·MMTA)$_a$ because of the steric hindrance of the methyl group. This study combines computational (high level ab initio) and experimental (crystallographic) evidence to demonstrate that the *endo* binding mode is more favorable and that it is due to the $C-H/\pi$ interaction between the methyl group of the MMTA and the central aromatic ring of the receptor. The complexation behavior of this host−guest system can be considered as an example of a noncovalent complex that exhibits *in*/*out* stereoisomerism, a concept originally introduced by Simmons and Park.[10] The *in*/*out* isomerism in covalently bonded systems has been reviewed by Alder and East.[11] The geometry of the 1:1 complexes[12] was fully optimized using the PM3 semiempirical SCF-MO method as implemented in the MOPAC-93 package[13] (see Figure 1). Moreover, with the purpose of evaluating the contribution of the $C-H/\pi$ interaction to the binding energy, we have optimized a complex between benzene and MMTA at the MP2/6-31+G* level of theory, imposing a C_3 symmetry, using the Gaussian 98 program.[14] Basis set superposition error (BSSE) was corrected by means of the counterpoise method.[15]

The intermolecular distance between the carbon atom of the methyl group and the centroid of the aromatic ring of the optimized benzene·MMTA complex is 3.49 Å, and the binding energy is −0.58 kcal/mol (see Figure 2). This binding energy compares well with previous calculation of complexes between benzene and methane using small basis sets.[7] It has been demonstrated[7] that small basis sets considerably underestimate the attraction compared with large ones in about 50%. Therefore, the contribution of the $C-H/\pi$ interaction to the total binding energy of the tripodal receptors is expected to be approximately 1 kcal/mol.

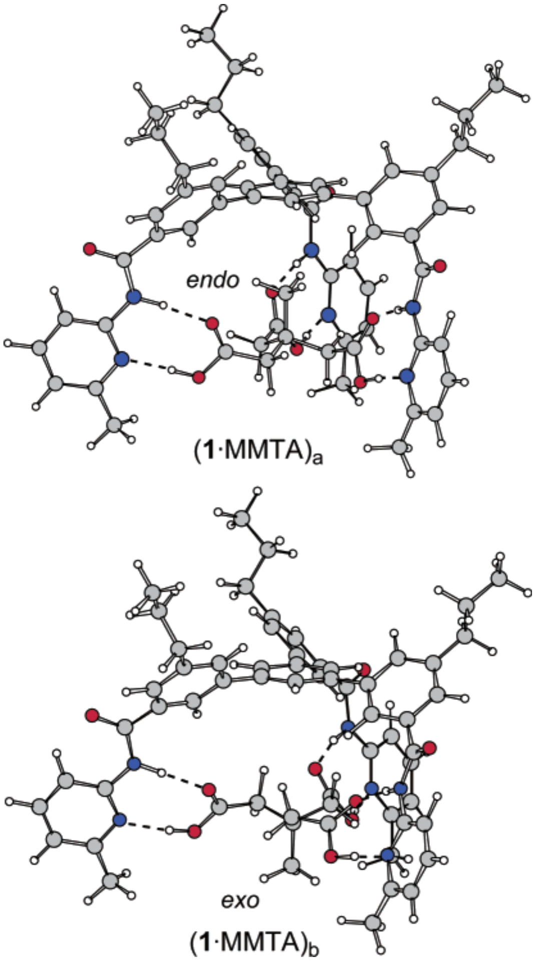

Figure 1. PM3 optimized structures of the two possible binding geometries.

To analyze the physical nature of the $C-H/\pi$ interaction and whether polarization is important, we have computed

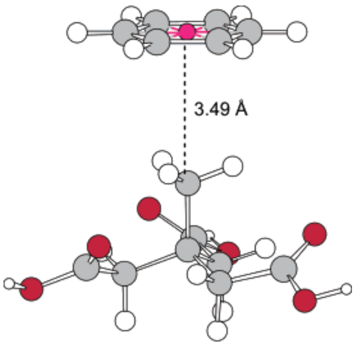

Figure 2. MP2/6-31+G* optimized geometry of the 1:1 complex.

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[10] (a) Simmons, H. E.; Park, C. H. *J. Am. Chem. Soc.* **1968**, *90*, 2428. (b) Park, C. H.; Simmons, H. E. *J. Am. Chem. Soc.* **1968**, *90*, 2429. (c) Park, C. H.; Simmons, H. E. *J. Am. Chem. Soc.* **1968**, *90*, 2431.

[11] Alder, W. A.; East, S. P. *Chem. Rev.* **1996**, *96*, 2111.

[12] Geomeries are available upon request by contacting tonif@soller.uib.es

[13] Stewart, J. J. P. *MOPAC-93*; Fujitsu Ltd., 1993.

its contribution to the total interaction energy using the recently developed Molecular Interaction Potential with polarization (MIPp),[16] which is a powerful tool for the prediction of binding properties of aromatic compounds.[17−19] MIPp is an improved generalization of the MEP where three terms contribute to the interaction energy: (i) an electrostatic term identical to the MEP,[20] (ii) a classical dispersion−repulsion term, and (iii) a polarization term derived from perturbational theory.[21] Therefore, it provides a natural partitioning of the interaction energy into intuitive components.

Calculation of the MIPp of benzene interacting with H$^+$ was performed using the HF/6-31+G* wave function. As a result, a MIPp minimum was found at 2.31 Å over the ring along the C_6 axis. In the calculations the H$^+$ was considered as a classical nonpolarizable particle. We have explored the electrostatic (E_e), polarization (E_p), and van der Waals (E_{vw}) energies at the minimum. Whereas the E_{vw} is small ($E_{vw} = -0.76$ kcal/mol), the other two components are -8.04 kcal/mol for E_e and -4.21 kcal/mol for E_p. These results point out the importance of the polarization component, which is approximately half of the electrostatic one. Additionally, we have also computed the MIPp of 1,3,5-triphenylbenzene optimized at the HF/6-31+G* level, to know if the other three aromatic rings have some influence over the molecular interaction potential inside the cavity. The minimum was found at 2.25 Å over the central ring with an energy value of -13.41 kcal/mol, 1.92 kcal/mol more negative than the one computed for benzene. Interestingly, in this case the polarization component is $E_p = -7.93$ kcal/mol, slightly higher than the electrostatic ($E_e = -6.40$ kcal/mol), probably a result of the effect of the supplementary aromatic rings. In Figure 3 we show the MIPp energy map of triphenylbenzene computed at 2.25 Å below the central ring.

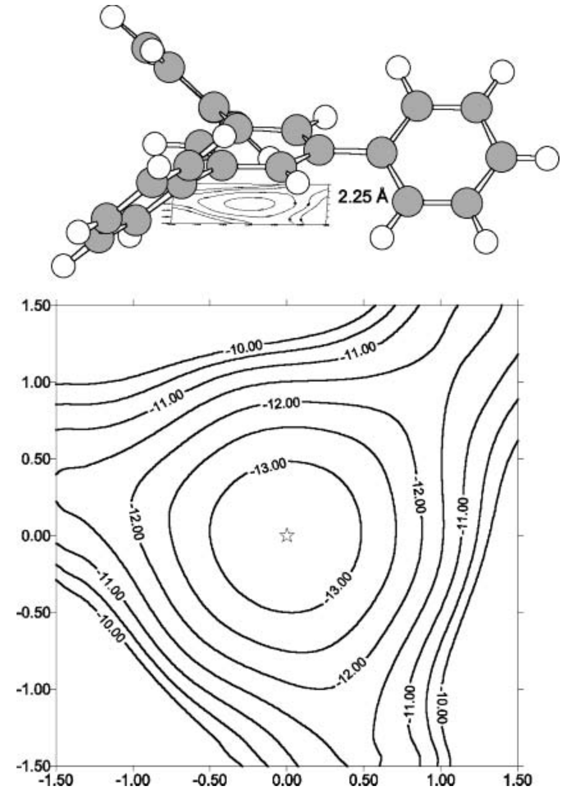

Figure 3. MIPp energy map at 2.25 Å from the central ring of triphenylbenzene.

Further evidence for this C−H/π interaction can be obtained from experimental results. Our group has recently reported[22] an experimental (NMR and X-ray) study of selective recognition of MMTA in organic solvents. The molecular X−ray structure that was obtained for the **1**·MMTA complex is reproduced in Figure 4. It corresponds to the *endo* geometry. It features a C_3 symmetry axis where the methyl group of the MMTA points toward the central aromatic ring of the receptor. The crystallographic distance between the carbon atom of the methyl group and the centroid of the aromatic ring is 3.50 Å, close to the computed distance of 3.49 Å and confirming the C−H/π interaction. In solution, variable temperature ^{1}H NMR experiments[22] were carried out to detect the existence of different complex geometries

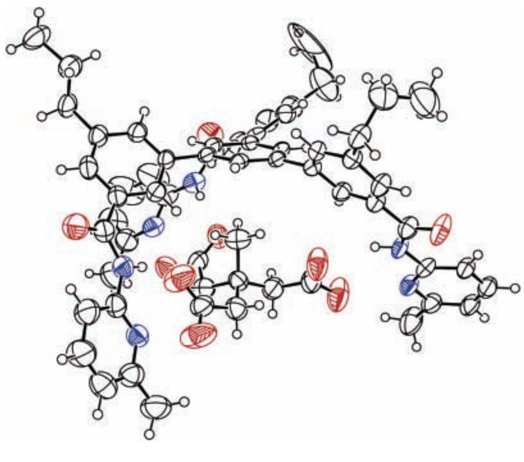

Figure 4. ORTEP drawing of the **1**·MMTA crystal structure. Thermal ellipsoids are drawn at the 50% probability level.

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(14) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery Jr., J. A.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O;. Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K;. Forestman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al−Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, Revision A.7; Gaussian, Inc.: Pittsburgh, PA, 1998.

(15) Boys, S. F.; Bernardi, F. *Mol. Phys.* **1970**, *19*, 553.

(16) Luque, F. J.; Orozco, M. *J. Comput. Chem.* **1998**, *19*, 866.

(17) Cubero, E.; Luque, F. J.; Orozco, M. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 5976.

(18) Quiñonero, D.; Frontera, A.; Suñer, G. A.; Morey, J.; Costa, A.; Ballester, P.; Deya, P. M. *Chem. Phys. Lett.* **2000**, *326*, 247.

(19) Quiñonero, D.; Garau, C.; Rotger, C.; Frontera, A.; Costa, A.; Ballester, P.; Deya,P. M. *Angew. Chem., Int. Ed*. **2002**, *41*, 3389.

(20) Scrocco, E.; Tomasi, J. *Top. Curr. Chem*. **1973**, *42*, 95.

(21) Francl, M. M. *J. Phys. Chem*. **1985**, *89*, 428.

(22) Ballester, P.; Capó, M.; Costa, A.; Deya, P. M.; Gomila, R.; Decken, A.; Deslongchamps, G. *J. Org. Chem*. **2002**, *67*, 8832.

in $CDCl_3$. The ^1H NMR signals did not show any sign of decoalescence in the range of temperatures from 280 to 220 K, providing evidence for the nonexistence of equilibrium processes. 1D NOE difference experiments at room and low temperatures confirmed the *endo* geometry of the complex. Furthermore, an upfield shift is observed for the methyl singlet signal of the MMTA in the complex because it feels the ring current effect of the central aromatic ring of the receptor.

In summary, this study shows that very weak nonbonded C−H/π interactions can influence the molecular recognition pattern in a host−guest system and that they should be taken into account even in the presence of stronger interactions. This has been illustrated by the example presented herein. Finally, the physical nature of the interaction has been studied using MIPp calculations.

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