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Complexation of adamantyl derivatives by a β–cyclodextrin dimer.

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Abstract

The binding constants, standard molar enthalpy, Gibbs free energy, and entropy changes were determined for the formation of complexes between adamantyl derivatives and a β-cyclodextrin dimer. It is concluded that, within experimental error, the two cyclodextrin residues in the dimer behave independent to each other when complexing the adamantyl derivatives.

Introduction

Supramolecular chemistry is mainly focused in designing new molecules which, after processes as recognition and assembling, form new identities denoted complexes, supramolecular assemblies, etc.[1] One well known example of a supramolecular entity is the formation of an host/guest complex between a cyclodextrin (the host) and an organic molecule (the guest) in which the organic molecule is located inside the cavity of the cyclodextrin.[2] In designing new systems which improve the efficiency or selectivity of the natural ones (for instance, the catalysis by enzymes), the first step is the knowledge of the energetic (as well as geometric) features among the interacting species. For that purpose, techniques as rotating-frame Overhauser enhancement spectroscopy (ROESY), which provides information on the complex structure, and Isothermal Titration Calorimetry (ITC), which allows the determination of basic thermodynamic parameters (ΔH, ΔS, ΔG and K_{eq}) and the stoichiometry of the complex in a single experiment, are nowadays routinely used in chemical laboratories.

The analysis of ITC experiments is straightforward when both guest and host are monotopic entities (i. e., both having one single site of interaction) since only one data analysis is possible.[3] However, several possibilities appear when (at least) one of the interacting species, is ditopic or polytopic in nature, since the sites can cooperatively interact or not. The knowledge of the microscopic equilibrium constants involved in the different equilibria will allow the determination of the existence of cooperativity (positive, negative or zero) between the different sites. Examples of the determination of microscopic binding contants in cyclodextrin systems have been given by Connors and Pendergast[4] when studying the complexation of sym-1,4-disubstituted benzenes, by Connors *et al*[5] for sym-4,4´-dibsubtituted biphenyls, and by Sur and Bryant[6] for porphyrins. In all these cases, the determination of the microscopic binding constants was possible since the two binding sites were identical and the relationships between microscopic and macroscopic binding constants is greatly simplified.

The complexation of adamantane derivatives with cyclodextrins has been the subject of numerous studies during the last twenty years.[7-27] This is due to several reasons. First, adamantane derivatives form strong complexes with β-cyclodextrin and the equlibrium constants are the strongest which can be found for the formation of this kind of inclusion complexes. This is because of the adamantyl residue perfectly fits inside the β-cyclodextrin cavity since the radius of this residue is slightly larger than the radius inside the cavity available for guest in this cyclodextrin. Second, unimers simultaneously having guest (adamantyl residue) and host (β-cyclodextrin residue) moieties in their structure have been obtained and by self-association formed linear supramolecular structure.[26] Third, adamantyl dimers have been synthesized and complexed with β-cyclodextrin dimers to form the so called "chelate complexes".[18] Fourth, adamantyl dimers have used to obtain linear and dentritic-like supramolecular polymers when they are complexed with polytopic hosts derived from β-cyclodextrin.[28-30] Finally, polytopic hosts and polytopic guests can be used to form other macromolecular assemblies.[31,32] In such cases, high viscosity enhancements have been observed, which are maximum for a composition in which the stoichiometry is one host (*β*CD residue):one guest (adamantyl residue).[33]

The aim of this paper is to study the complexation of several adamantyl derivatives by the β-cyclodextrin dimer shown in Figure 1, in order to check the existence or not of cooperative effects during the complexation process.

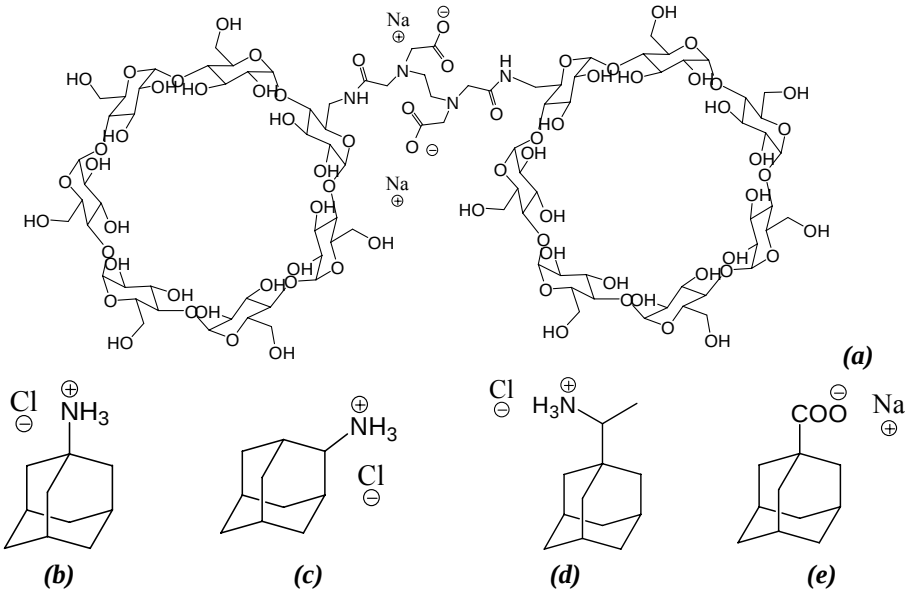

Figure 1.- (a) Structure of β-CD dimer derivative (βCD_2EDTA). (b) 1-adamantylammonium chloride. (c) 2-adamantylammonium chloride. (d) Rimantidine chloride. (e) Sodium 1-Adamantanecarboxylate.

Results and Discussion

Figure 2 shows typical experimental enthalpograms for the complexation of guests of Figure 1 with the βCD_2EDTA dimer. The fitting of the experimental results to the "single set of identical sites" model[34] leads to the fitting parameter values given in Table 1. It must be remembered that according to this model the equilibrium constant corresponds to the equilibrium

$$M + X \rightleftharpoons MX$$

and *n* is the number of sites. It can be noticed that *n* values are close to the expected stoichiometry for a complex formed by a ditopic host and a monotopic guest. On the other hand, equilibrium constants and ΔH^o values are in agreement with those obtained for similar systems.[7] Because of the *n* value, the experimental results were also fitted to a "two

sets of independent sites" model. The obtained values for the thermodynamic parameters are given in Table 2.

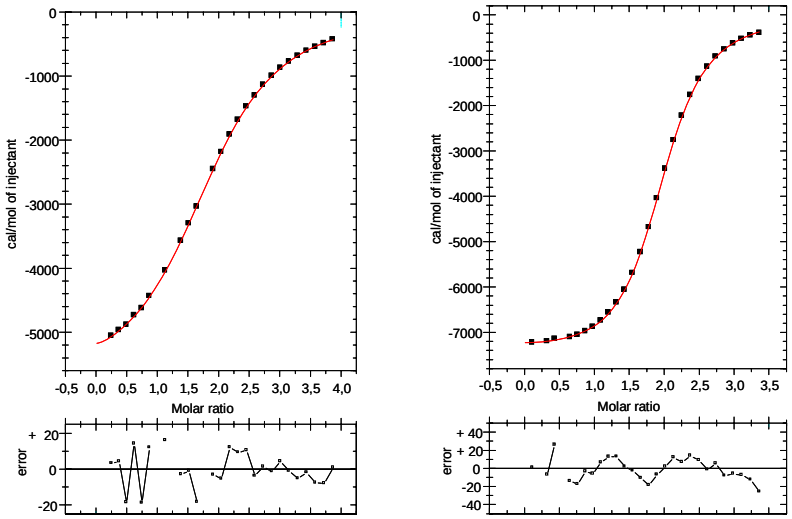

Figure 2.- Examples of calorimetric titration enthalpograms**. (a)** Injection of 10 μL aliquots of [2-AdNH_3Cl]=10.27 mM into the sample cell containing [CD-AEDT-CD]=0.623mM. **(b)** Injection of 10 μL aliquots of [Rimantidine]=11.06 mM into the sample cell containing [CD-AEDT-CD]=0.771 mM. Experiments were carried out at; T = 30,01ºC; pH= 7,55 phosphate buffer (50mM) to ensure ionization of any functional group, amine or carboxylate. Lines correspond to fit experimental results to stepwise (macroscopic) model for biding of two guests to the host. The fitting parameters are given in Table 1.

Table 1.- Thermodynamic parameters obtained by the "one set of binding sites model" from ITC experiments. T = 30,01ºC; pH= 7,55 phosphate buffer (50mM) to ensure ionization of functional groups, (amine or carboxylate).

Guest	***n***	$Log(K_{eq} / M^{-1})$	$\Delta G^0 / kJmol^{-1}$	$\Delta H^0 / kJmol^{-1}$	$T\Delta S^0 / kJmol^{-1}$
1-AdCOONa	1.98±0.01	4.22±0.11	-24.72±0.93	-27.03±0.57	-3.18±1.22
1-AdNH_3Cl	1.96±0.03	3.83±0.06	-22.23±0.33	-24.30±0.39	-2.13±0.66
2-AdNH_3Cl	1.94±0.01	3.82±0.04	-22.18±0.22	-26.18±0.94	-2.67±0.95
Rimantidine	1.95±0.02	4.31±0.18	-25.01±0.92	-30.85±0.74	-5.24±0.85

Table 2.- Thermodynamic parameters from ITC data fitted with a "two sets of independent sites model" for biding of two guests to the host.

Proceso 1:1	$K_1 / 10^4 M^{-1}$	$Log(K_1 / M^{-1})$	$\Delta G_1^0 / kJmol^{-1}$	$\Delta H_1^0 / kJmol^{-1}$	$T\Delta S_1^0 / kJmol^{-1}$	K_1 / K_2
1-AdCOONa	6.17±0.51	4.79±0.08	-27.8±0.4	-26.4±0.9	1.3±0.6	5.5±0.5
1-AdNH_3Cl	1.44±0.05	4.16±0.03	-24.2±0.2	-22.5±1.2	1.7±0.7	3.8±0.1
2-AdNH_3Cl	1.32±0.22	4.12±0.11	-23.9±0.6	-22.8±0.6	1.8±0.4	3.8±0.6
Rimantidine	5.84±0.07	4.8±0.1	-26.8±0.3	-31.4±0.9	2.2±0.3	3.7±0.1
Proceso 2:1	$K_2 / 10^3 M^{-1}$	$Log(K_2 / M^{-1})$	$\Delta G_2^0 / kJmol^{-1}$	$\Delta H_2^0 / kJmol^{-1}$	$T\Delta S_2^0 / kJmol^{-1}$	
1-AdCOONa	11.2±0.8	4.05±0.03	-23.7±0.7	-26.1±0.8	-4.9±0.9	
1-AdNH_3Cl	3.80±0.08	3.58±0.02	-20.7±0.1	-23.4±0.5	-4.4±1.1	
2-AdNH_3Cl	3.47±0.12	3.54±0.02	-20.5±0.1	-25.6±0.9	-5.1±1.4	
Rimantidine	15.8±0.5	4.19±0.02	-24.2±0.6	-29.3±0.8	-5.7±0.2	

The complexation process is shown in Figure 3. Although four microscopic equilibrium constants are involved only three equilibrium constants are independent since the obvious relationship $K_{1x} \cdot K_{12} = K_{2x} \cdot K_{22}$ applies.

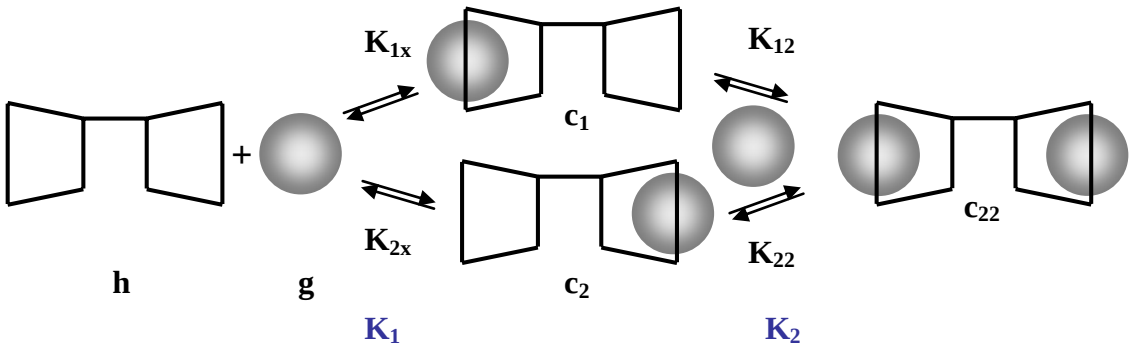

Figure 3.- Schematic microscopic description of the complexation process.

The relationships between the equilibrium constants are given by

$$K_1 = K_{1x} + K_{2x} \qquad 1/K_2 = 1/K_{12} + 1/K_{22}$$

For the present dimer, both sites are identical and, consequently, $K_{1x} = K_{2x}$ and $K_{12} = K_{22}$. Previous equations lead to $K_1 = 2K_{1x}$ and $K_2 = K_{22}/2$.

The site-specific interaction parameter is defined as $\alpha = K_{12}/K_{2x} = K_{22}/K_{1x}$.[35] Under the condition of two independent binding sites, $K_{1x} = K_{22}$ and $\alpha = 1$. Therefore, $K_1/K_2 = 4$. In order of self-consistency of the analysis of the experimental results, this should be the value obtained for the K_1/K_2 relationship. Table 2 shows that except for the negatively charged guest 1-AdCOONa (although it is possible that in this case the value is affected by some undetected bias), the K_1/K_2 values are close to the expected ones. Therefore, it can be concluded that, within experimental error, the two cyclodextrin residues in the dimer behave independent to each other when complexing adamantyl derivatives.

ITC measurements.

The description of the thermodynamic background for ITC experiments can be found elsewhere[3] and experimental procedure in the MicroCalc calorimeter instructions. ITC experiments were carried out at 30.00 (0.01 °C). Experimental titration curves were analyzed with the MCS Origin ITC 5.0 program delivered with the instrument. Average

values of the thermodynamic parameters and their standard deviations were calculated from 2-3 experimental runs.

The synthesis of the β–cyclodextrin dimer can be found elsewhere.[36]

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References

1. Lehn, J.-M. *Supramolecular Chemistry*; VCH: Weinheim, 1995.
2. Szejtli, J. *Cyclodextrin Technology*; Kluwer Academic Publishers: Dordrecht, The Nederlands, 1988.
3. M. J. Blandamer in *Biocalorimetry. Applications of Calorimetry in the Biological Sciences*; Ladbury, J. E.; Chowdhry, B. Z. Ed., Wiley & Sons: Chichester, 1998; Vol. chapter one.
4. Connors, K. A.; Pendergast, D. D. *J. Am. Chem. Soc.* **1984**, *106*, 7607.
5. Connors, K. A.; Paulson, A.; Toledo-Velasquez, D. *J. Org. Chem.* **1988**, *53*, 2023.
6. Sur, S. K.; Bryant, R. G. *J. Phys. Chem.* **1995**, *99*, 4900.
7. Soto Tellini, V. H. ; Jover, A.; Carrazana, J.; Galantini, L.; Meijide, F.; Vázquez Tato, J. *J. Am. Chem. Soc*. **2006**, *128*, 5728.
8. Matsui, Y.; Mochida, K. *Bull. Chem. Soc. Jpn.* **1978**, *51*(3), 673-6.
9. Harrison, J. C. ; Eftink, M. R. *Biopolymers* **1982**, *21*, 1153.
10. Gelb, R. I.; Schwartz, L. M.; Laufer, D. A. *J. Chem. Soc., Perkin Transactions 2* **1984**, 15.
11. Cromwell, W. C.; Bystrom, K.; Eftink, M. R. *J. Phys. Chem.* **1985**, *89*, 326.
12. Selvidge, L. A. ; Eftink, M. R. *Anal. Biochem.* **1986**, *154*, 400.
13. Jannasch, R. *Pharmazie* **1986**, *41*, 478.
14. Briggner, L. E.; Ni, X. R.; Tempesti, F.; Wadsoe, I. *Thermochim. Acta* **1986**, *109*, 139.
15. Eftink, M. R.; Andy, M. L.; Bystrom, K.; Perlmutter, H. D.; Kristol, D. S. *J. Am. Chem. Soc.* **1989**, *111*, 6765.
16. Gelb, R. I.; Schwartz, L. M. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1989**, *7*, 537.
17. Palepu, R.; Reinsborough, V. C. *Aust. J. Chem.* **1990**, *43*, 2119.
18. Zhang, B.; Breslow, R. *J. Am. Chem. Soc.* **1993**, *115*, 9353.
19. Gelb, R. I.; Raso, S.; Alper, J. S. *Supramol. Chem.* **1995**, *4*, 279.
20. Ruediger, V.; Eliseev, A.; Simova, S.; Schneider, H.-J.; Blandamer, M. J.; Cullis, P. M.; Meyer, A. J. *J. Chem. Soc., Perkin Trans. 2* **1996**, 2119.
21. Godinez, L. A.; Schwartz, L.; Criss, C. M.; Kaifer, A. E. *J. Phys. Chem. B* **1997**, *101*, 3376.
22. Linnemayr, K.; Rizzi, A.; Allmaier, G. *J. Chromatogr. A* **1997**, *791*, 299.
23. Blandamer, M. J.; Cullis, P. M.; Engberts, J. B. F. N. *J. Chem. Soc., Faraday Trans.* **1998**, *94*, 2261.
24. Vashi, P. R.; Cukrowski, I.; Havel, J. *S. Afr. J. Chem.* **2001**, *54* , 84.
25. Carrazana, J.; Jover, A.; Meijide, F.; Soto, V. H.; Vázquez Tato, J. *J. Phys. Chem.* **2005**, *109* , 9719.
26. Tellini, V. H. S.; Jover, A.; Galantini, L.; Meijide, F.; Tato, J. V. *Acta Crystal.B* **2004**, *B60*, 204.
27. Harries, D.; Rau, D. C.; Parsegian, V. A. *J Am Chem Soc.* **2005,** *127***,** 2184.
28. Miyauchi, M.; Hoshino, T.; Yamaguchi, H.; Kamitori, S.; Harada, A. *J. Am. Chem. Soc.* **2005**, *127*, 2034.
29. Hasegawa, Y.; Miyauchi, M.; Takashima, Y.; Yamaguchi, H.; Harada, A. *Macromolecules* **2005**, *38*, 3724.
30. Ohga, K.; Takashima, Y.; Takahashi, H.; Miyauchi, M.; Kawaguchi, Y.; Yamaguchi, H.; Harada, A. *Chem. Lett.* **2005**, *34*, 320.
31. Amiel, C.; Moine, L.; Sandier, A.; Brown, W.; David, C.; Hauss, F.; Renard, E.; Gosselet, M.; Sebille, B. *ACS Symp. Ser. (Stimuli-Responsive Water Soluble and Amphiphilic Polymers)* **2001**, *780*, 58.
32. Wenz, G.; Weickenmeier, M.; Huff, J. *ACS Symp. Ser. (Associative Polymers in Aqueous Media)* **2000**, *765*, 271.
33. Gosselet, N. M.; Beucler, F.; Renard, E.; Amiel, C.; Sebille, B. *Colloids Surf., A* **1999**, *155*, 177.
34. *Origin . ITC Data Analysis in Origin, Tutorial Guide*, versión 5.0, **1998**

35. E. di Cera, "*Thermodynamic Theory of Site-Specific Binding Processes in Biological Macromolecules*", Cambridge University Press, 2005.
36. Alvarez, M.; Antelo, A.; Jover, A.; Meijide, F.; Gancedo, C.; Galantini, L.; Vázquez Tato, J. *J. Inclusion Phenom. Macrocycl. Chem.* **2009**, *63*, 309.