

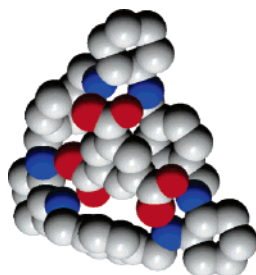
Shape-Complementarity in the Recognition of Tricarboxylic Acids by a [3+3] Polyazacyclophane Receptor

Jana Hodačová,^{*,†} Martin Chadim,[†] Jiří Závada,[†] Juan Aguilar,[‡] Enrique García-España,^{*,‡} Santiago V. Luis,^{*,§} and Juan F. Miravet[§]

Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Flemingovo nám. 2, 166 10 Prague 6, Czech Republic, Departamento de Química Inorgánica, Instituto de Ciencia Molecular, Universidad de Valencia, C/Dr. Moliner 50, 46100 Burjassot, Valencia, Spain, and Departamento de Química Inorgánica y Orgánica, UAMOA, Universitat Jaume I/CSIC, 12080 Castellón, Spain

hodacova@uochb.cas.cz; enrique.garciaes@uv.es; luiss@qio.uji.es

Received November 11, 2004



The interaction of a macrocycle containing three *trans*-(1*R*,2*R*)-diaminocyclohexane units connected by *p*-xylene spacers with the isomers 1,3,5-benzenetricarboxylic (1,3,5-BTC), 1,2,4-benzenetricarboxylic (1,2,4-BTC), and 1,2,3-benzenetricarboxylic (1,2,3-BTC) acids and their relevant anions is studied by means of potentiometric and NMR analysis. The interaction is highest for the isomer 1,3,5-BTC, which perfectly fits within the macrocyclic cavity of the host species. The studies have been extended to the triacid 1,3,5-benzenetricarboxylic observing in this case the effect of a size mismatch between host and guest species.

Introduction

Recognition of carboxylic acids is a goal of paramount relevance in supramolecular chemistry due to their ubiquitous presence in biological systems.¹ Therefore, over the two past decades a great amount of experimental work has been devoted to address this point.^{2–4} This goal is particularly challenging when the solvent of the choice is water due to its buffering effect on charge–charge electrostatic attractions and to its role handicapping the formation of direct hydrogen bonds between host and guest species.⁵ Thereby, receptors that fit very well electronically and stereochemically with a given substrate have to be built. Here we present the case of the

macrocyclic **L**, which presents three *trans*-(1*R*,2*R*)-diaminocyclohexane units interconnected by *p*-xylene spacers (Chart 1).

This receptor containing a symmetrical 3-fold arrangement of functional groups seems to be well suited for the recognition of complementarily arranged guests such as 1,3,5-trisubstituted rigid aromatic guests.

Results and Discussion

Binding Studies. The synthesis of **L** has been achieved by [3+3] cyclocondensation of terephthaldehyde with

[†] Academy of Sciences of the Czech Republic.

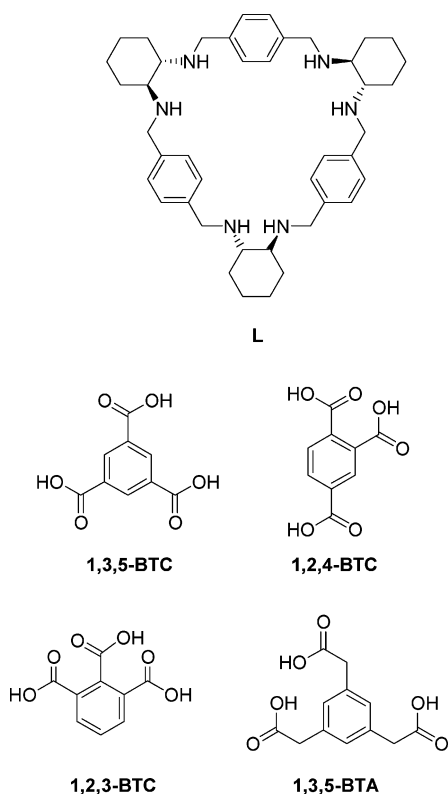
[‡] Universidad de Valencia.

[§] Universitat Jaume I/CSIC.

(1) (a) Dietrich, B.; Hosseini, M. W.; Lehn, J.-M.; Sessions, R. B. *J. Am. Chem. Soc.* **1981**, *103*, 1282–1283. (b) Hosseini, M. W.; Lehn, J.-M. *J. Am. Chem. Soc.* **1982**, *104*, 3525–3527. (c) Hosseini, M. W.; Lehn, J.-M. *Helv. Chim. Acta* **1986**, *69*, 587–603. (d) Kimura, E.; Sakonaka, A.; Yatsunami, T.; Kodama, M. *J. Am. Chem. Soc.* **1981**, *103*, 3041–3045. (e) Kimura, E.; Kodama, M.; Yatsunami, T. *J. Am. Chem. Soc.* **1982**, *104*, 3182–3187.

(2) (a) Rossi, S.; Kyne, G. M.; Turner, D. L.; Wells, N. J.; Kilburn, J. D. *Angew. Chem., Int. Ed.* **2002**, *41*, 4233. (b) Alfonso, I.; Dietrich, B.; Gotor, V.; Lehn, J.-M. *Helv. Chim. Acta* **2001**, *84*, 280. (c) Ballester, P.; Capó, M.; Costa, A.; Deyá, P. M.; Gomila, R.; Decaen, A.; Deslongchamps, G. *Org. Lett.* **2001**, *3*, 267. (d) Choi, H.-J.; Park, Y. S.; Yun, S. H.; Kim, H.-S.; Cho, C. S.; Ko, K.; Ahn, K. H. *Org. Lett.* **2002**, *4*, 795. (e) Cutland, A. D.; Halfen, J. A.; Kampf, J. W.; Pecoraro, V. L. *J. Am. Chem. Soc.* **2001**, *123*, 6211. (f) Shinoda, S.; Tadokoro, M.; Tsukubu, H.; Arakawa, R. *Chem. Commun.* **1998**, 181. (g) Bencini, A.; Bianchi, A.; Burguete, M. I.; Doménech, A.; García-España, E.; Luis, S. V.; Paoli, P.; Ramírez, J. A. *J. Chem. Soc., Perkin Trans. 2* **1994**, 569. (h) Dietrich, B. *Pure Appl. Chem.* **1993**, *65*, 1457.

CHART 1



trans-(1*R*,2*R*)-diaminocyclohexane followed by reduction of the macrocyclic hexamine, using NaBH₄. The one-pot procedure gave **L** in 90% yield.⁶

pH-metric titrations carried out in water on the interaction of **L** in its protonated forms with the anions derived from the three isomers 1,2,3-benzenetricarboxylic, 1,2,4-benzenetricarboxylic, and 1,3,5 benzenetricarboxylic acids (hereafter 1,2,3-BTC, 1,2,4-BTC, and 1,3,5-BTC) as well as those of 1,3,5-benzenetriacetic acid (hereafter 1,3,5-BTA) (see Chart 1) are presented in Table 1.

The results collected in the table show the formation of H_xAL^(x-3) adduct species with protonation degrees, *x*, that vary from 4 to 7 for the system **L**-1,2,3-BTC, from 3 to 8 for the system **L**-1,2,4-BTC, from 2 to 8 for the system **L**-1,3,5-BTC, and from 3 to 5 for the system **L**-1,3,5-BTA.

(3) (a) Ait-Haddou, H.; Wiskur, S. L.; Lynch, V. M.; Anslyn, E. V. *J. Am. Chem. Soc.* **2001**, *123*, 11296. (b) Wiskur, S. L.; Anslyn, E. V. *J. Am. Chem. Soc.* **2001**, *123*, 10109. (c) Niikura, K.; Anslyn, E. V. *J. Org. Chem.* **2003**, *68*, 10156–10157.

(4) For a recent review on receptors for carboxylic acid and carboxylate anions: Fitzmaurice, R. J.; Kyne, G. M.; Douheret, D.; Kilburn, J. D. *J. Chem. Soc., Perkin Trans. 1* **2002**, 841.

(5) For an analysis of the different forces contributing to the stabilization of anion complexes, see for instance: (a) Schneider, H.-J.; Theis, I. *Angew. Chem., Int. Ed.* **1989**, *28*, 753. (b) Schmidtchen, F. P. In *Supramolecular Chemistry of Anions*; Bianchi, A., Bowman-James, K., Garcia-España, E., Eds.; Wiley-VCH: New York, 1997; Chapter 4. (c) Bianchi, A.; Garcia-España, E. In *Supramolecular Chemistry of Anions*; Bianchi, A., Bowman-James, K., Garcia-España, E., Eds.; Wiley-VCH: New York, 1997; Chapter 6. (d) Gale, P. A. *Coord. Chem. Rev.* **2001**, *213*, 79.

(6) (a) Gawronski, J.; Kolbon, H.; Kwit, M.; Kartusiak, A. *J. Org. Chem.* **2000**, *65*, 5768. (b) Chadim, M.; Buděšínský, M.; Hodačová, J.; Závada, J.; Junk, P. C. *Tetrahedron: Asymmetry* **2001**, *12*, 127. (c) Gao, J.; Martell, A. E. *Org. Biomol. Chem.* **2003**, *1*, 2795.

TABLE 1. Logarithms of the Stability Constants for the Interaction of **L** with 1,2,3-BTC, 1,2,4-BTC, 1,3,5-BTC, and 1,3,5-BTA (A) Determined in 0.15 M NaCl at 298.1 K

reaction	1,2,3-BTC	1,2,4-BTC	1,3,5-BTC	1,3,5-BTA
A ³⁻ + L + 2H ⁺ = H ₂ AL ⁻			21.0(2)	
A ³⁻ + L + 3H ⁺ = H ₃ AL		29.37(5)	29.98(4)	28.99(5)
A ³⁻ + L + 4H ⁺ = H ₄ AL ⁺	33.64(5) ^a	34.62(5)	35.49(4)	33.86(6)
A ³⁻ + L + 5H ⁺ = H ₅ AL ²⁺	38.65(2)	39.48(4)	40.58(3)	38.85(2)
A ³⁻ + L + 6H ⁺ = H ₆ AL ³⁺	42.66(2)	43.45(4)	43.93(4)	
A ³⁻ + L + 7H ⁺ = H ₇ AL ⁴⁺	46.25(3)	46.73(5)	46.76(4)	
A ³⁻ + L + 8H ⁺ = H ₈ AL ⁵⁺		49.43(6)	49.33(7)	
A ³⁻ + H ₃ L ³⁺ = H ₃ AL		3.56	4.16	3.18
A ³⁻ + H ₄ L ⁴⁺ = H ₄ AL ⁺	3.52	4.50	5.37	3.75
HA ²⁻ + H ₃ L ³⁺ = H ₄ AL ⁺	2.43	3.73	5.04	3.10
HA ²⁻ + H ₄ L ⁴⁺ = H ₅ AL ²⁺	3.13	4.28	5.82	3.78
H ₂ A ⁻ + H ₃ L ³⁺ = H ₅ AL ²⁺	3.54	4.89	6.48	3.94
A ³⁻ + H ₅ L ⁵⁺ = H ₅ AL ²⁺	4.65	5.48	6.59	4.85

^a Values in parentheses are standard deviations in the last significant number.

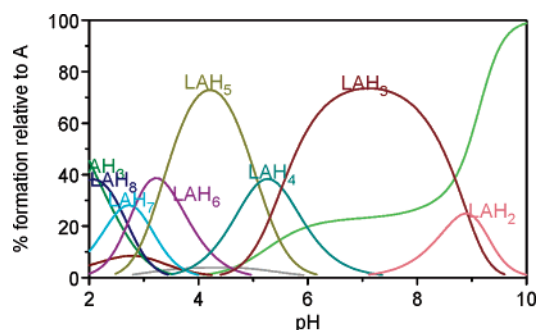


FIGURE 1. Distribution diagram for the system **L**-1,3,5 {[**L**] = [1,3,5-BTC] = 10⁻³ M}.

The species distribution diagram *vs* pH of the system **L**-1,3,5-BTC plotted in Figure 1 for a 1:1 molar ratio **L**:1,3,5-BTC ([**L**] = [1,3,5-BTC] = 10⁻³ M) shows that H₃AL and H₅AL²⁺ (A³⁻ = 1,3,5-benzenetricarboxylate trianion) are the species which predominate in aqueous solution at a larger extent.

Taking into account the protonation constants of **L** (Table 1)^{6c} and 1,3,5-BTC (see the Supporting Information),^{2g} it can be confidently stated that H₃AL should be the result of the reaction of the fully deprotonated carboxylate trianion (A³⁻) with the triprotonated receptor (H₃L³⁺):



This reasoning also holds for analogous triprotonated species in the system **L**-1,2,4-BTC for which log *K* = 3.55 can be inferred.

However, this kind of analysis cannot be applied to the more protonated adducts since at their pH range of formation both receptor and anions are involved in overlapping protonation equilibria. Therefore, we had suggested that the use of conditional stability constants defined as

$$K_{\text{cond}} = \frac{\sum [H_{i+j}AL]}{\sum [H_iA] \sum [H_jL]}$$

is particularly useful.⁷ This, on the other hand, permits us to compare different systems and get the correct selectivity ratios just by dividing the conditional constants obtained for those systems at the selected pH values. Figure 2 shows plots of the logarithms of the

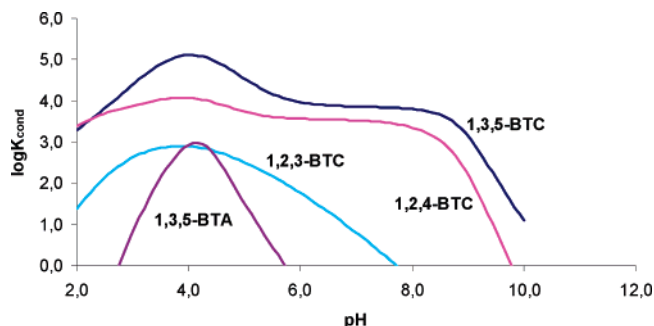


FIGURE 2. Plot of the conditional stability constants for the systems L-1,3,5-BTC, L-1,2,4-BTC, L-1,2,3-BTC, and L-1,3,5-BTA.

conditional constants vs pH for the systems under study.

It can be seen that the conditional constants follow the sequence 1,3,5-BTC-L > 1,2,4-BTC-L > 1,2,3-BTC-L > 1,3,5-BTA-L.

Particularly noticeable is the 2 orders of magnitude difference found between the constants of the systems 1,3,5-BTC-L and 1,2,3-BTC-L. At pH 4 the conditional constants would be $\log K = 5.11$ and 2.89 for the systems L-1,3,5-BTC and L-1,2,3-BTC, respectively. The conditional stability constants for the system L-1,2,4-BTC present an intermediate value ($\log K = 4.07$ at pH 4).

In the case of 1,3,5-BTA the measured interaction reaches a maximum value of ca. $\log K_{\text{ef}} = 3.0$ at pH 4 where the H_5AL^{2+} species predominates. However, the binding is much weaker for the other pH values. This difference can be at least partly ascribed to the higher basicity of 1,3,5-BTA, which reduces the charge-charge interaction between receptor and guest at a given pH value.

NMR Studies. To understand the factors which determine this selectivity, we have performed a NMR study on these systems. The one-dimensional ^1H NMR spectra of L consists in the aromatic region of a singlet signal, which, at pH 6.4, appears at 7.37 ppm and integrates for the 12 protons of the benzene rings. Addition of equimolar amounts of 1,2,3-BTC, 1,2,4-BTC, and 1,3,5-BTC produces increasing upfield shifts of $\Delta\delta = 0.03$, 0.05 , and 0.12 ppm, respectively (see Figure 3A). These shifts, which are not due to a partial protonation of the receptor as it is checked by the lack of variation of the signals of the benzylic protons in the different spectra (Figure 3B), can be attributed to edge-to-face $\pi-\pi$ aromatic interactions between the host and guest species that will be important for the case of 1,3,5-BTC in agreement with the modeling (see below).⁸

Interestingly enough, NOESY experiments show cross-peaks between the singlet signal of 1,3,5-BTC and the

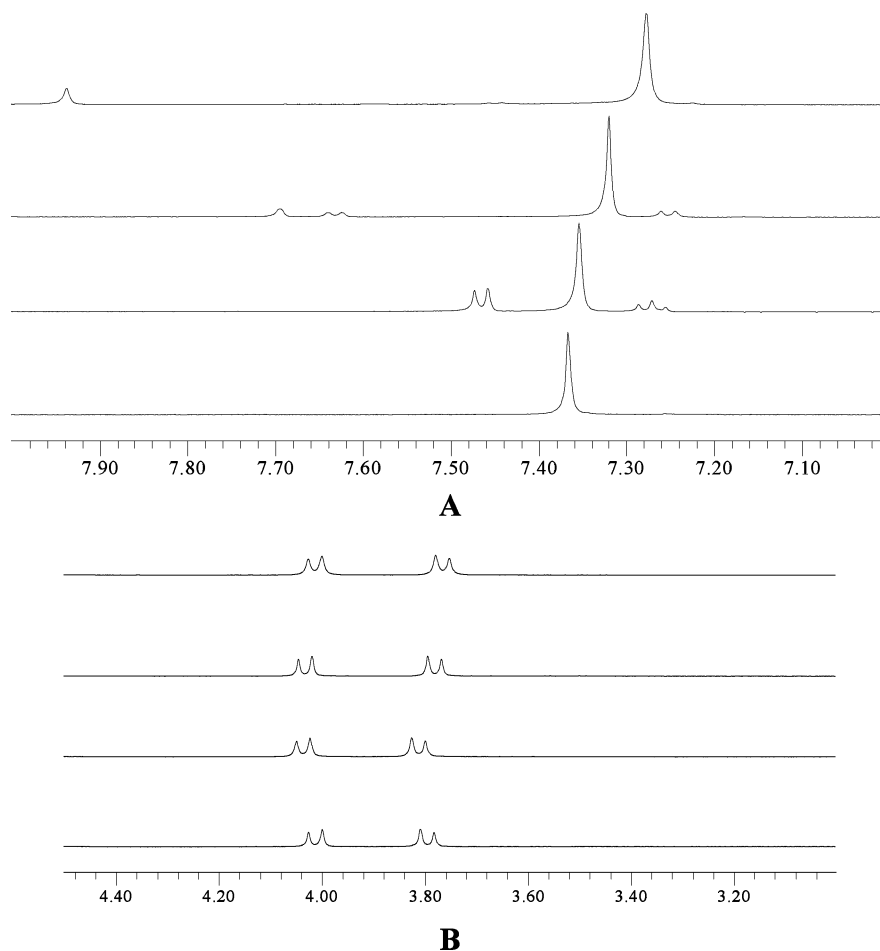


FIGURE 3. (A) Aromatic region of the ^1H NMR spectra at pH 6 of the systems L (bottom spectrum), L-1,2,3-BTC, L-1,2,4-BTC, and L-1,3,5-BTC (upper spectra). (B) Benzylic protons in the ^1H NMR spectra at pH 6 of the systems L (bottom spectrum), L-1,2,3-BTC, L-1,2,4-BTC, and L-1,3,5-BTC (upper spectra).

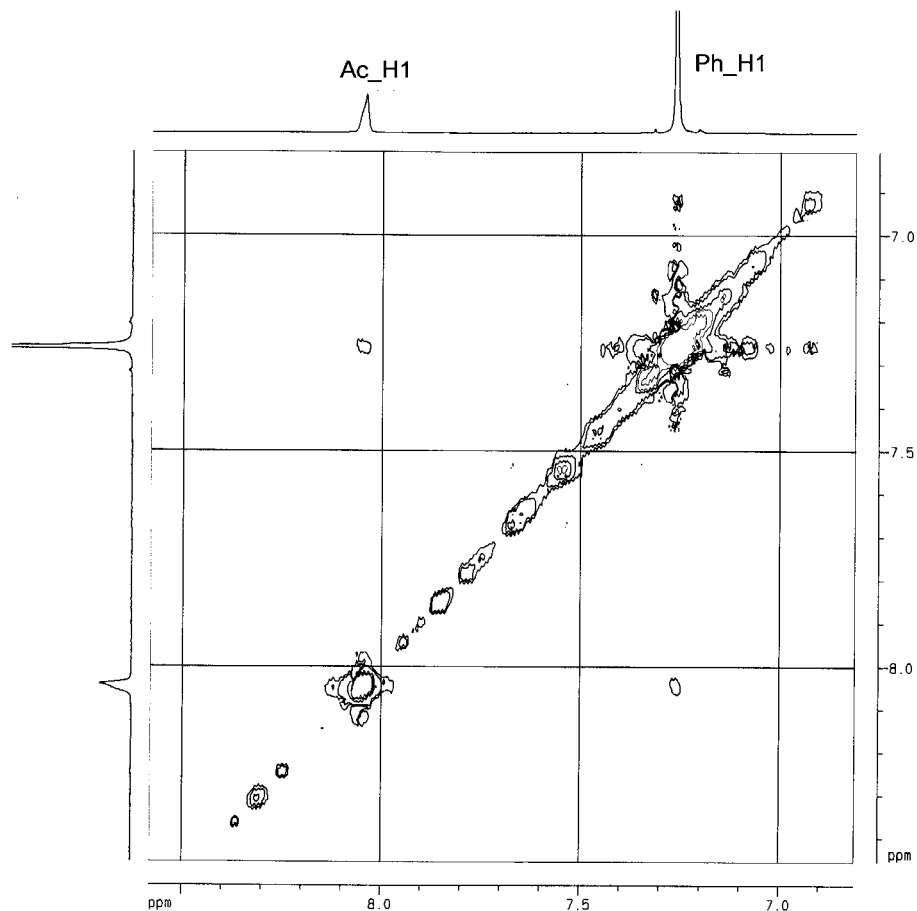
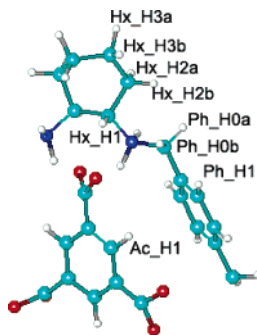


FIGURE 4. NOESY spectrum for the system L-1,3,5-BTC at pH 6.4 showing the aromatic region.

TABLE 2. Estimated Distances from the NOESY Experiments for the System 1,3,5-BTC-L

	Ac_H1	Ph_H1	Ph_H0b	Ph_H0a	Hx_H1	Hx_H2b	Hx_H3b	Hx_H2a	Hx_H3a
Ac_H1		3.83	npf	npf	4.87	npf ^a	npf	npf	nd
Ph_H1			3.26	3.26	3.671	nd ^b	npf	npf	npf
Ph_H0b				1.816	3.50	3.36	npf	4.85	npf
Ph_H0a					3.13	3.37	npf	3.51	npf
Hx_H1						3.21	npf	nd	nd
Hx_H2b							3.48	nd	nd
Hx_H3b								nd	nd
Hx_H2a									nd
Hx_H3a									

^a npf = no observed cross-peak. ^b nd = nondetermined due to overlapping cross-peaks.



signal of the aromatic protons of the receptor (Figure 4). The analysis of the ROESY and NOESY spectra have allowed for deriving the distances shown in Table 2.

The calculated model using the constraints obtained from the NMR analysis of the system L-1,3,5-BTC provides the picture shown in Figure 5. 1,3,5-BTC would

be disposing almost coplanar to the macrocyclic cavity in order to maximize the interaction between their complementary parts.

Although neither ROESY nor NOESY cross-peaks are observed between the doublet or the triplet signals of the aromatic protons of 1,2,3-BTC or 1,2,4-BTC and those of

TABLE 3. Estimated Distances from the NOESY Experiments for the System 1,3,5-BTA-L

	Ac_H1	Ac_Hb	Ph_H1	Ph_H0b	Ph_H0a	Hx_H1	Hx_H2b	Hx_H3b
Ac_H1		2.2	2.7	npf	npf	npf	npf	npf
Ac_Hb ^b	2.2	–	2.1	npf	npf	npf	npf	npf
Ph_H1			–	2.3	2.2	npf	npf	npf
Ph_H0b				–	1.8	2.3	2.1	npf
Ph_H0a					–	2.3	2.2	npf
Hx_H1						–	2.5	Npf
Hx_H2b							–	2.4

^a npf = no observed cross-peak. ^b Ac_Hb refers to the benzylic hydrogens of BTA.

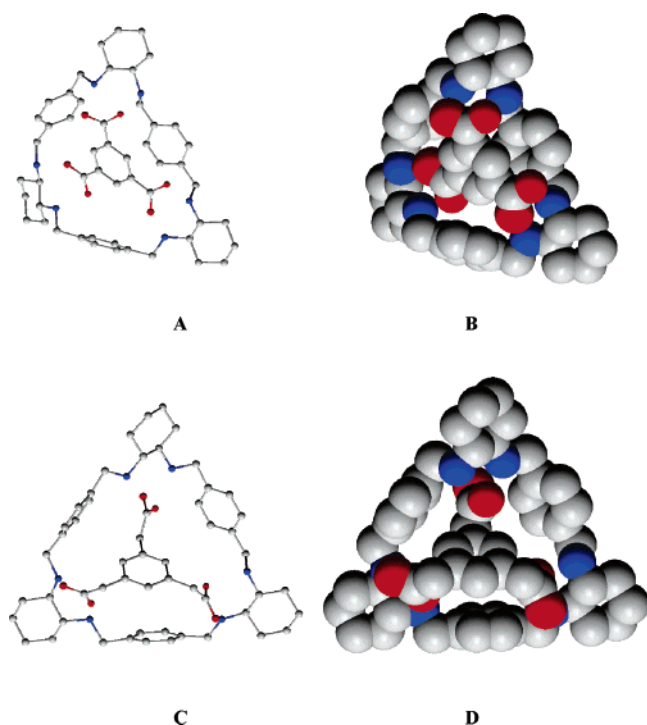


FIGURE 5. Ball and stick and CPK molecular models for the system H_3L^{3+} and the tricarboxylate anions derived from 1,3,5-BTC (A and B) and from 1,3,5-BTA (C and D).

the aromatic part of the host, the intramolecular cross-peaks allow for inferring that **L** has a similar disposition as in the system **L**-1,3,5-BTC. This limited flexibility of **L** would explain the decreased interaction of **L**-1,2,3-BTC with respect to **L**-1,3,5-BTC. To achieve a maximum interaction 1,2,3-BTC would need to orient its aromatic ring more perpendicular with respect to the cavity of the receptor. Therefore, the NMR data and modeling suggest that such an almost 2 orders of magnitude difference between the constants of the systems **L**-1,3,5-BTC and **L**-1,2,3-BTC can be attributed to a perfect fitting between the shape of 1,3,5-BTC and the macrocyclic structure (Figure 5).

In the case of 1,3,5-BTA, which shows the lowest constants under our experimental conditions, NOESY and ROESY show, however, the presence of intermolecular cross-peaks between the aromatic protons of the host and guest species similar to those found for 1,3,5-BTC although of lower intensity. Intramolecular cross-peaks suggest an analogous receptor conformation to that inferred for the other systems. Nevertheless, to fit the distance restraints derived from the NMR experiments the acid has to adopt a disposition in the cavity much

more distorted and cannot match as well the complementary binding sites of the receptors (see Figure 5C,D). Table 3 collects some representative distances calculated from the NMR data.

Conclusions

The interaction of **L** with different tricarboxylic acids containing aromatic subunits constitutes a very nice example of molecular recognition in water based on shape/function complementarity that very nicely exemplifies the Emil-Fischer lock and key principle.⁹ 1,3,5-BTC, the guest which best matches electronically and stereochemically the relatively rigid host species, gives one of the largest selectivities reported in water ($\Delta(\log K)$ ca. 2.0 for 1,3,5-BTC-L over 1,2,3-BTC-L and for 1,3,5-BTC-L over 1,3,5-BTA-L at pH 4).

Experimental Section

Ligand **L** was prepared according to the literature procedure.^{6c}

Emf Measurements. All pH-metric measurements ($\text{pH} = -\log [H^+]$) employed for the determination of protonation and stability constants were carried out in 0.15 M NaCl solutions at 298.1 ± 0.1 K, using the equipment and the methodology already described.¹⁰ The program HYPERQUAD was employed to compute the protonation constants of **L** of the triacids 1,2,3-BTC, 1,3,5-BTC, 1,2,4-BTC, and 1,3,5-BTA and the formation constants of the adducts AH_xL (A^{3-} = tricarboxylate trianions).¹¹

NMR Studies. The 1H and ^{13}C NMR spectra were recorded on a 300 MHz NMR spectrometer operating at 299.95 MHz for 1H and at 75.43 for ^{13}C . For the ^{13}C NMR spectra, dioxane was used as a reference standard (δ 67.4 ppm) and for the 1H spectra the solvent signal. NOESY and ROESY were recorded at three different mixing times, 200, 500 and 700 ms (pH 6.4, $T = 298$ K), on a 500 MHz NMR spectrometer operating at 500.130 MHz. Adjustments to the desired pH were made by using drops of DCl or NaOD solutions. The pD was calculated from the measured pH values with the following correlation, $\text{pH} = \text{pD} - 0.4$.¹³

From NOESY experiments, distances were estimated assuming that the relationship Vr^6 keeps almost constant, V being the NOESY cross-peak volume and r the distance between two protons.¹³ The volume of the cross-peak for the geminal protons Ph_H0a and Ph_H0b was taken as a reference

(7) Albelda, M. T.; Bernardo, M. A.; García-España, E.; Godino-Salido, M. L.; Luis, S. V.; Melo, M. J.; Pina, F.; Soriano, C. *J. Chem. Soc., Perkin Trans. 2* **1999**, 2545.

(8) Meyer, E. A.; Castellano, R. K.; Diederich, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1210–1250.

(9) (a) Fischer, E. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 2611. (b) Fischer, E. *Ber. Dtsch. Chem. Ges.* **1894**, *27*, 2985.

(10) García-España, E.; Ballester, M.-J.; Lloret, F.; Moratal, J.-M.; Faus, J.; Bianchi, A. *J. Chem. Soc., Dalton Trans.* **1988**, 101.

(11) Gans, P.; Sabatini, A.; Vacca, A. *Talanta* **1996**, *43*, 1739.

(12) Convington, A. K.; Paabo, M.; Robinson, R. A.; Bates, R. G. *Anal. Chem.* **1968**, *40*, 700.

and a distance of 1.816 Å between them was used for the calculations. A model corresponding to an energy minimum was obtained by molecular mechanics calculations with the program HYPERCHEM 6.03, using MM+ as the force-field and constraining the distances (Ph_H1)–(Ac–H1) and (Hx_H1)–(Ph_H0b) to 3.8 and 3.5 Å, respectively.

Acknowledgment. Financial support from the Spanish Dirección General de Enseñanza Superior (Projects

(13) (a) Jeener, J.; Meier, B. H.; Bachmann P.; Ernst, R. R. *J. Chem. Phys.* **1979**, *71*, 4546–4553. (b) Wagner, R.; Berger, S. *J. Magn. Reson.* **1996**, *123 A*, 119–121.

BQ2003-0215-CO3 and GV-Grupos-03/196 and GV04B-225) and from the Academy of Sciences (Z4 055 905) and the Grant Agency of the Czech Republic (203/01/0067) is gratefully acknowledged.

Supporting Information Available: Tables of protonation constants and NOESY experiments. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO048000V