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Mutually induced formation of host-guest complexes between *p*-sulfonated calix[8]arene and photolabile cholinergic ligands

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Alexandre Specht, Philippe Bernard, Maurice Goeldner* and Ling Peng*

[*] Prof. Dr. M. Goeldner, A. Specht
CNRS UMR 7514, Laboratoire de Chimie Bio-organique

Dr. P. Bernard
CNRS UMR 7081, Laboratoire de Pharmacochimie de la Communication Cellulaire
Faculté de Pharmacie
Université Louis Pasteur Strasbourg
BP 24, 67401 Illkirch cedex
France
Fax: Int. code + 390 244 306
Email: goeldner@bioorga.u-strasbg.fr

Dr. L. Peng
Chemistry Department, Wuhan University, P. R. China
and AFMB CNRS UMR 6098, 13009 Marseille, France
Fax : Int. code + 4 91 82 94 91
Email: ling@afmb.cnrs-mrs.fr

NMR Analysis

Job's plot:

The stoichiometry of the complexes was determined from Job's plots of chemical shifts of complex as a function of the molar fraction of guest, by keeping constant the sum of the total concentrations of host and guest (6.0×10^{-4} M) while varying the molar fraction of the guest from 0 to 1.

Concentration effect:

NMR spectra were taken with different concentrations of complex. The solutions of complex were prepared with different concentrations of guest (from 9.15×10^{-5} to 2.00×10^{-2} M), by using large excess of host in order to ensure over 96% complex formation between the guest and the host. The chemicals shifts of both the guest and the host were concentration-independent.

A series of NMR titration experiments were carried out with different concentrations of guest (from 9.15×10^{-5} to 9.15×10^{-4} M). The experimental data were fitted with the curves for 1:1 bimolecular complex [1] and gave the same binding constants and the same maximal chemical upfield shifts (Table 3).

Table 2: Maximal chemical upfield shifts ($\Delta\delta$, ppm) of ligand **1** and association constants (K_A, M^{-1}) of complex [**A-1**] obtained by NMR titration with different concentrations of **1**.

$[\mathbf{1}]_0$	$\Delta\delta_{\text{N-Me}_3}$	$K_{A,\text{ N-Me}_3}$
9.15×10^{-5} M	0.97	27.8
3.00×10^{-4} M	0.95	28.6
9.15×10^{-4} M	0.95	26.3

2D-NMR analysis:

For the complex [**A-1**], NOE signals between aromatic proton and methyl proton of ammonium group were observed. To determine the distance between the aromatic moiety and the cationic ammonium group of **1** in the complex [**A-1**], we used a NOESY sequence [2] with mixing time varying from 10 ms to 500 ms. A distance of 4 Å, between one proton of the cationic ammonium group and the *para*-H of the aromatic moiety in **1**, was deduced from the NMR data, using the distance between two vicinal aromatic protons as a reference.

Molecular Modeling

Guest 1: The lowest energy conformations of **1** were found by means of the Sybyl Systematic Search Option with a 10° increment. [3] Each conformer was minimized as above described and the energy was used to select the best conformer. The same operation was repeated with an intramolecular distance constraint of 4 Å, between one proton of the cationic

ammonium group and the *para*-H of the aromatic moiety in **1**, deduced from experimental NMR data of [**A-1**]. A gain of energy of about 3 kcal/mol was resulted for the selected conformer with constraint (-18 kcal/mol) compared to the one without constraint (- 21 kcal/mol) (Figure 4). Finally, the folded conformer was used in the docking study with the host **A**.

Host A: The minimization procedure did not affect the two structures of **A**, compared to the crystallographic coordinates. Indeed, when taking the aromatic carbon atom coordinates of each crystal, Dovhif [4] and Foztix,[5] with their homologous atoms on the respective generated structures of **A**, the RMSD of the pleated loop conformer and the pinched conformer were 0.75 Å and 0.66 Å, respectively. These two conformers were used for the docking study.

Complex [**A-1**]: The docking of **1** with the pleated loop conformer of **A**, revealed no real complexes. Indeed, in this conformation, **A** formed a plane with a high degree of organization. In this conformation, **1** was not able to form interactions either with the hydrogen bond network or with the aromatic ring of **A**. The docking of **1** with the pinched conformer of **A** resulted in two docking solutions: (i) **1** was placed across the annular ring formed by the aromatic moieties in **A**. In this solution, the distance constraint on **1** was lost during the minimization. (ii) **1** was placed inside the annular cavity, as shown in Figure 3 in the text. In this solution, the aromatic part and the cationic ammonium part of **1** were 3.7 Å apart and inserted concomitantly inside two aromatic pockets formed by the calix[8]arene structure. Moreover, the sulfonate group did shift outside of the annular ring and allow an optimal positioning of the aromatic part of **1**. Interestingly, the conformation of **1** is conserved along the minimization of the complex. In the complex, the aromatic part of **1** formed a stacking with one of the eight aromatic groups in **A** whereas the cationic ammonium part of **1** formed a π-cation interaction with another aromatic moiety in **A**.

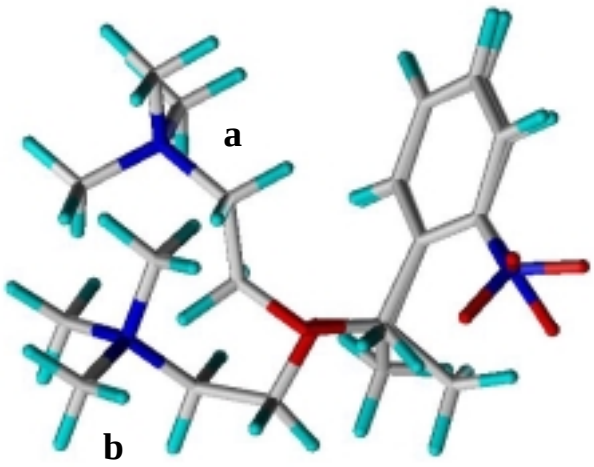

Figure 4: Superimposed structures of the ligand **1** (**a**) in the constrained conformation in the complex [**A-1**] by molecular modeling and (**b**) in the relaxed conformation in crystal state.

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