DOI: 10.1002/ejoc.201000729

Molecular Tweezers: Synthesis and Formation of Host–Guest Complexes

Béatrice Legouin,[a] Maud Gayral,[a] Philippe Uriac,[a] Jean-François Cupif,[a] Nicolas Levoin,[b] Loic Toupet,[c] and Pierre van de Weghe*[a]

Keywords: Supramolecular chemistry / Host-guest systems / Pi interactions / Molecular recognition

A chiral molecular tweezer obtained from (+)-usnic acid placed in solution in the presence of various aromatic compounds afforded complexes with low association constants. Thus, the X-ray structure of assembly **3i** is presented, where the guest is sandwiched between the two pincers of the tweezer. The association constants for various guests were determined through different methods. Finally, other tweezers with electron-rich aromatic aldehydes and ketones were prepared from (1*R*,2*R*)-1,2-diaminocyclohexane. The most interesting complexes were also confirmed through structural analysis, and the best results were obtained with 10-hydroxyphenanthrene-9-carbaldehyde (**5i**) as the aromatic moiety.

Introduction

The process of molecular recognition of guest molecules by a synthetic host is of great interest in supramolecular chemistry and depends on the nature of the intermolecular interactions. For this reason the study and characterization of these interactions have experienced enormous growth in recent years. Among the different intermolecular forces, noncovalent aromatic interactions are of particular relevance. The π–π-stacked aromatic interactions have been found to govern diverse molecular organizations in both solution and the solid state. Furthermore, this is considered as a very important component of ligand–receptor interactions, particularly in medicinal chemistry.[1] However, in comparison to more conventional interactions such as hydrogen bonds, ion pairs, and hydrophobic interactions, the π–π-stacked interaction is not clear, and to date, no commonly useful model has been built to interpret properly the experimental observations. This could be due to the complication of the π–π-stacked dependency on substituent groups, variable geometries, and the cooperative effect of various noncovalent interactions. Therefore, study of a variety of systems involved in π–π-stacked interactions is an important step toward a better understanding of this type of noncovalent interaction.

Whitlock first reported the synthesis of molecular tweezers and their use as suitable models to bind aromatic guests.[2] Molecular tweezers are simple molecular hosts that can be described by the presence of two tethered pincers by a more or less rigid spacer. With a distance of about 7 Å between electron-rich or electron-poor aromatic pincers, molecular tweezers appear to be an ideal model to study noncovalent aromatic interactions.[3] We recently synthesized novel chiral molecular tweezer **1** by using (+)-usnic acid as the tethered pincer and (1*R*,2*R*)-1,2-diaminocyclohexane as the spacer (Figure 1) and showed its ability to form a host–guest complex with 2,4,7-trinitro-9*H*-fluoren-9-one (TNF; **2a**).[4] Here we first reported the determination of association constants of host–guest complexes from **1** with different common guest aromatic compounds substituted with strong electron-withdrawing groups. The association constants *K* in molecular complexes in solution were determined by ^{1}H NMR[5] and UV/Vis spectroscopy.[6] We then extended this approach by describing the synthesis of new potential molecular tweezers from (1*R*,2*R*)-1,2-diaminocyclohexane and various carbonyl derivatives aiming to obtain better tweezers.

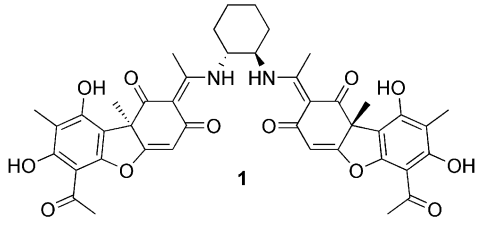


Figure 1. Structure of chiral molecular tweezer **1**.

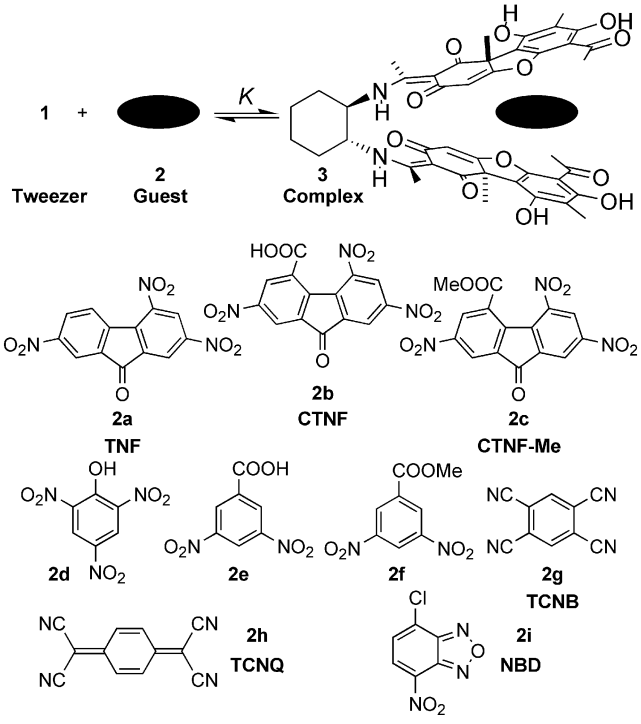
[a] EA Substances Lichéniques et Photoprotection, Faculté des Sciences Biologiques et Pharmaceutiques,
Université de Rennes 1,
2 av. du Prof. Léon Bernard, 35043 Rennes Cedex, France
Fax: +33-2-23234425
E-mail: pierre.van-de-weghe@univ-rennes1.fr
[b] Bioprojet-Biotech,
4 rue du Chenay Beauregard, BP 96205, 35762 Saint-Grégoire, France
[c] GM CM, CNRS UMR 6509, Université de Rennes 1, Campus de Beaulieu,
35042 Rennes Cedex, France

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201000729.

Results and Discussion

Determination of Association Constants of Host–Guest Complexes from 1 with Electron-Poor Aromatic Guests

Due to its electron-rich pincers, molecular tweezer **1** could form stable complexes **3** with different electron-demanding aromatic derivatives **2** in solution involving π–π interactions (Scheme 1). The binding ability of **1** with regard to a variety of aromatic derivatives was first evaluated by ^{1}H NMR titration in CD_2Cl_2 at 298 K. No signal of the free species in the spectrum was observed, suggesting that the rate of complexation and decomplexation are fast under these conditions (time-average signals with 500 MHz ^{1}H NMR). In most cases, significant shifts of the peaks ascribable to **1** and aromatic derivatives **2** were observed. Relying on our previous study, the 1:1 stoichiometry of the complexes was considered and confirmed for complex **3a** in CH_2Cl_2 on the basis of the UV/Vis Job's plot[7] as shown in Figure 2. The association constants of **3** were determined by a nonlinear curve-fitting analysis from ^{1}H NMR spectroscopy and are reported in Table 1.



Scheme 1. Formation of host–guest complexes **3**.

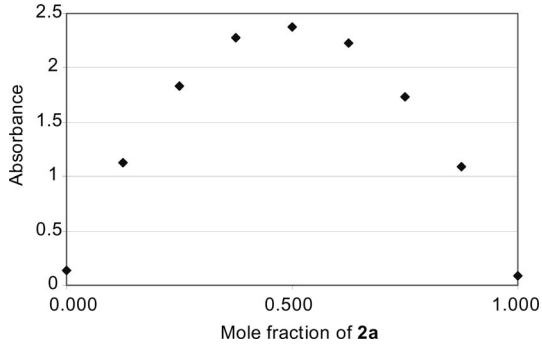


Figure 2. Plot of Job's method for a mixture of **1** and **2a** ([**1**] + [**2a**] = 20 mM) at 450 nm (solvent: CH_2Cl_2).

Weak complexes **3a**–**g** and **3i** were obtained by mixing molecular tweezer **1** with electron-deficient aromatic derivatives **2a**–**g** and **2i**; the association constants determined by NMR spectroscopy were found to be between 7 and 53 M^{-1}. These results allow the following conclusions: Complex **3a** obtained from TNF (**2a**) is substantially more stable than corresponding complexes **3b**–**g** by a factor of at least 2. We believed we could improve the affinity of **1** for electron-poor aromatic guests by combining H-bonding with π–π interactions as reported sometimes for cucurbituril host–guest systems.[8] However, carboxylic acids **2b** and **2e** and phenol **2d** only led to weak complexes **3** ($15 < K < 26$ M^{-1}). On the other hand, the data indicate the influence of the steric hindrance of guests **2** to the stability of complexes **3**. As observed, the addition of a methyl ester group or a carboxylic acid function to starting fluorenone derivative **2a** decreased the strength of the association for complexes **3**. A similar comparison could be done between assembly **3e** and **3f**, acid **2e** affording a more stable complex. Although the association constants of complexes **3a**–**g** and **3i** are weak, the use of the ^{1}H NMR titration method allowed us to have a better idea of the affinity of the guests with the tweezer. For compound **3h**, the signal intensity decreased but no chemical shift change was observed during

Table 1. Values of association constants K (500 MHz NMR in CD_2Cl_2, UV/Vis in CH_2Cl_2).

Entry	**3**	Association constant K [M^{-1}, 298 K]		
		^{1}H NMR ($\Delta\delta_{max}$, Hz)	UV/Vis, Method A[a] (ε, $L\,mol^{-1}\,cm^{-1}$)	UV/Vis, Method B[b] (ε, $L\,mol^{-1}\,cm^{-1}$)
1	**3a**	53 ± 1 (272 ± 1)	27 (1250)	35 ± 4 (1100 ± 100)
2	**3b**	26 ± 2 (252 ± 8)	45 (1500)	31 ± 5 (2000 ± 200)
3	**3c**	16 ± 1 (194 ± 5)	23[c] (1500)	22 ± 3[c] (1600 ± 170)
4	**3d**	15 ± 1 (271 ± 11)	12 (13400)	14 ± 3 (11800 ± 2200)
5	**3e**	22 ± 1 (326 ± 5)	18 (750)	20 ± 1 (750 ± 100)
6	**3f**	7 ± 1 (308 ± 25)	21 (750)	24 ± 5 (700 ± 100)
7	**3g**	10 ± 1 (103 ± 3)	8 (1600)	11 ± 3 (1300 ± 150)
8	**3h**	n.d.[d]	n.d.[d]	24 ± 7 (2800 ± 500)
9	**3i**	9 ± 0.3 (233 ± 4)	n.d.[d]	n.d.[d]

[a] Determined by the Benesi–Hildebrand method. [b] Determined by a curve-fitting procedure. [c] Determined at 440 nm, otherwise determined at 450 nm. [d] n.d. = not determined.

the NMR titration; the latter did not then allow the determination of the association constant. Therefore, we also decided to evaluate the association constants by using UV/Vis spectroscopy and to compare those results with the previous one obtained by ^{1}H NMR titration.

Molecular tweezer **1** and guests **2** lead to colorless or pale yellow solutions. This color changes when guest molecule **2** is added to a solution of **1** in methylene chloride; the appearance of a more or less intense color during the process of association results from charge-transfer bands. Because of its simplicity of implementation, the graphical Benesi–Hildebrand method[9] (method A) was first used to determine the association constants. The spectroscopic data were obtained from solutions in methylene chloride by varying the concentration of tweezer **1** while the concentration of guest **2** was held constant. The equation of the plot 1/[**1**] vs. [**2**]/A gives 1/$K\varepsilon$ as the intercept and 1/ε as the slope, where ε is the molar extinction coefficient of complex **3**. Due to the weak values of constants and to avoid negative value of the intercept, the concentrations of **1** and **2** were carefully defined.[10,11] Unfortunately, we were not able to determine the association constant of **3h** due to the presence of absorption bands of **2h** in the same area as those of charge transfer (450 nm). It is also important to note that due to the low values of the association constants, this graphical method is too vague and is a source of errors. In order to have more precise values of K and finally to evaluate the association constant of complex **3h**, we decided to determine the association constant by treating the experimental data with nonlinear analysis (method B).[12]

The results of the UV/Vis determination of K are given in Table 1. The association constants calculated by both methods A and B are self-consistent considering the precision of the results. The use of method B allowed us to determine the association constant of complex **3h**. Therefore, method B appears more satisfactory than method A, as it can overcome the problem of recovery of the characteristic charge-transfer bands of the complex with one of the starting materials. A comparison of the results obtained from ^{1}H NMR spectroscopy with the spectrophotometric data shows a greater incertitude with the latter. However, conclusions on the behavior of guests is quite similar whatever the method concerned; the association constant of **3a** remained the strongest, provided that the inversion of the K values of **3a** and **3b** by using the Benesi–Hildebrand method was ignored.

Crystals of complex **3i** suitable for X-ray diffraction analysis were obtained by slow evaporation of dichloromethane at room temperature from an ethanol/dichloromethane (1:1) solution (Figure 3). X-ray crystal analysis of **3i** shows that 4-chloro-7-nitro-2,1,3-benzoxadiazole (NBD; **2i**) is sandwiched between the two usnic acid units, as reported for complex **3a**.[4] The centroid distances in **3i** between adjacent usnic acids and **2i** are 3.701 and 3.619 Å. These values are consistent with those expected for π–π-stacking interactions. While the centroid distance between each aromatic ring of pincers is 7.486 Å in **1**,[4] the distance in complex **3i** decreases to 7.247 Å and to 6.900 Å in complex **3a**.[4] The presence of a guest in the molecular tweezer reduces the distance between both usnic acid units and appears to be proportional to the value of the association constant of the complex: 2.6 ± 0.2 M^{-1} at 298 K for molecular tweezer **1** alone,[13] weaker for assembly **3i** (9 ± 0.3 M^{-1} at 298 K), and better for complex **3a** (53 ± 1 M^{-1} at 298 K).

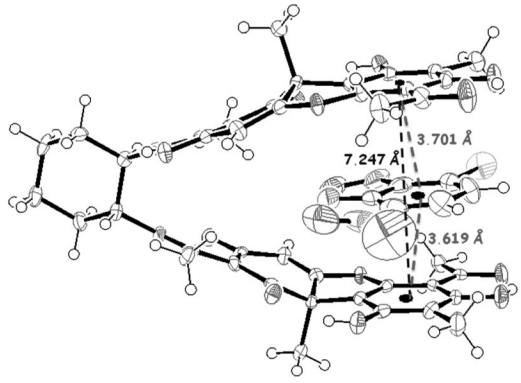


Figure 3. X-ray structure of complex **3i** (molecules of CH_2Cl_2 that are present in the crystals were voluntarily omitted to simplify the figure, >50% probability level).

During this work we also investigated the possibility of forming complexes through noncovalent aromatic interactions between usnic acid and TNF. Whatever the method of analysis used, NMR or UV/Vis spectroscopy, no evidence suggests the presence of these π–π stacked aromatic interactions between usnic acid and TNF. This observation indicates that the presence of a tether such as *trans*-1,2-diaminocyclohexane is essential, probably to limit entropy loss associated with the binding event.

In this first part, we showed that chiral molecular tweezer **1** prepared from (+)-usnic acid could form host–guest complexes with a variety of electron-poor aromatic derivatives. The binding strength of these complexes varies between 7 and 53 M^{-1} after evaluating by ^{1}H NMR titrations and between 11 and 35 M^{-1} from spectrophotometric data (method B). The correlation of these association constants with the help of spectrophotometric and NMR methods shows a quite similar order of the guests. However, the values of the association constants are too weak to obtain a good correspondence between both methods.

Synthesis of New Molecular Tweezers from (1*R*,2*R*)-1,2-Cyclohexanediamine

With a centroid–centroid distance around 7.4Å and 14.23° as angle formed between the planes of the two aromatic rings, molecular tweezer **1** has good characteristics for the construction of molecular assemblies. However, we wanted to determine whether tweezer **1** can be simplified by replacing the usnic acid by a residue such as acetophenone or benzaldehyde derivatives. Consequently, several important points have to be checked (Figure 4): (1) By changing the mode of bonding between the spacer and the pincer (an imine function instead of the keto enamine system in

the case of usnic acid) the stability of the resulting derivatives could be different. Is the presence of an *o*-hydroxy function to stabilize the imine function by a hydrogen bond essential? (2) The use of acetophenone and benzaldehyde derivatives as pincers can lead to compounds that have similar structures to the salen ligands.[14] Which elements favor spatial arrangement of the aromatic groups that lead to a tweezer and not a salen-type system?

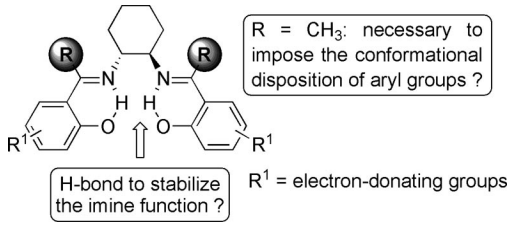
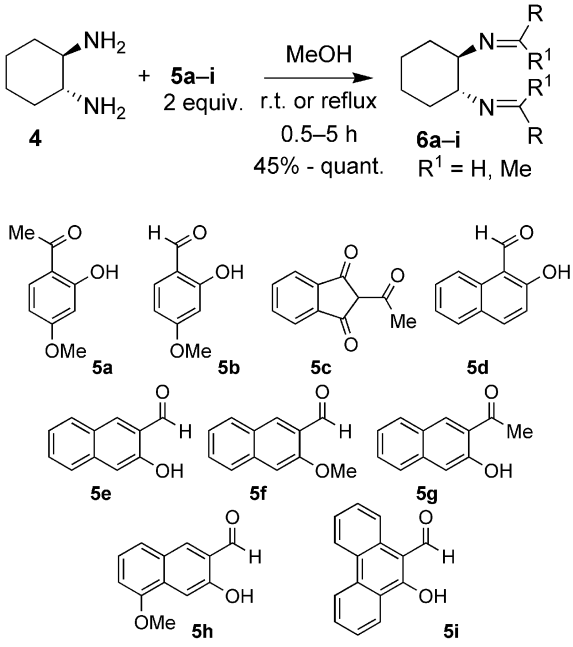


Figure 4. Conception of potential molecular tweezers.

In order to prepare these new potential tweezers, several aromatic ketones and aldehydes bearing a phenol function or a methyl group in the *ortho* position were selected. (1*R*,2*R*)-1,2-Diaminocyclohexane (**4**) in the presence of these carbonyl derivatives **5** (2 equiv.) in methanol at room temperature or reflux afforded expected imines **6** in moderate to excellent yields (Scheme 2 and Table 2). The presence of the hydroxy group in the *ortho* position of the carbonyl seems to be essential for the formation and for the stability of **6**, as aldehyde **5f**[15] bearing a methoxy group instead of a phenol function did not lead to substrate **6f**. 2-Acetyl-1,3-indanedione (**5c**) was also engaged in this study due to the formation of a keto enamine bond with the diaminocyclohexane that is quite similar to the tweezer obtained from usnic acid.



Scheme 2. Synthesis of new potential molecular tweezers **6**.

Table 2. Synthesis of **6** and values of association constants *K* with TNF (**2a**).

Entry	6	Yield [%]	Tweezer[a]	*K* [M^{-1}][b] ($\Delta\delta_{max}$, Hz)
1	**6a**	61	no	–
2	**6b**	quant.	no	–
3	**6c**	85	no	–
4	**6d**	85	no	–
5	**6e**	78	yes	7 ± 0.4 (206 ± 8)
6	**6f**	n.r.[c]	–	–
7	**6g**	45	yes	5.9 ± 0.5 (392 ± 28)
8	**6h**	87	yes	8 ± 0.4 (502 ± 18)
9	**6i**	86	yes	24 ± 1 (592 ± 15)

[a] Evaluation by ^{1}H NMR spectroscopy. [b] Determined by ^{1}H NMR spectroscopy (500 MHz) at 298 K, 1:1 stoichiometry of the complexes in CD_2Cl_2. [c] No reaction.

In order to determine if products **6** can act as tweezers in the presence of aromatic derivatives we developed a rapid test by using ^{1}H NMR spectroscopy. By adding 1 equiv. of TNF (**2a**; corresponding to a concentration of 2 mM) to 30 equiv. of **6**, the formation of a molecular assembly could be monitored by upfield or downfield shifts of the proton signals of **2a**.

We first prepared compounds **6a** and **6b** that have structures very close to those of the previously reported Schiff bases obtained from **4** and 2-hydroxyacetophenone and salicylaldehyde.[16] The X-ray structures obtained from these described compounds showed a centroid–centroid distance of 7.20 and 6.51 Å, respectively, but the angle formed between the planes of the two aromatic rings is 83.13° for the first substrate and 56.46° for the second. These very open angles are probably the reason[17] why compounds **6a** and **6b** do not seem to give molecular assemblies with **2a** (Table 2, Entries 1 and 2). 2-Acetyl-1,3-indanedione (**5c**) combined with **4** afforded in good yield expected product **6c**, for which crystals suitable for X-ray diffraction were obtained. Compound **6c** did not seem to form a host–guest assembly, as evidenced by the NMR test and foreshadowed by the data obtained from X-ray analysis of **6c** (the centroid–centroid distance is 8.569 Å and the angle formed between the planes of the two aromatic rings is 71.40°). This was confirmed by the isolation of crystals formed from an equimolar mixture of **6c**/**2a**, whose X-ray structure shows that **2a** is not included in **6c** (Figure 5).

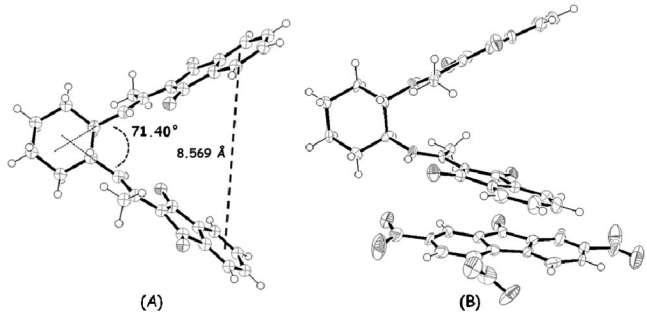


Figure 5. X-ray structures of compound **6c** (A) and mixture of **6c**/**2a** (B).

We were also interested in forming potential tweezers from naphthyl derivatives to increase the surface of the pincers so that they could better interact with **2a** to improve the formation of the molecular assemblies. 2-Hydroxynaphthalene-1-carbaldehyde (**5d**), in the presence of **4**, led to **6d** in good yield and afforded crystals suitable for X-ray analysis (Figure 6). The aromatic moieties are properly oriented, and the centroid–centroid distance is 7.728 Å (view A), but the angle between the planes of the two aromatic rings is wide open (84.48°) and the aromatic overlapping is limited to only one ring (view B), which probably results in a lack of interaction with **2a** as shown by ^{1}H NMR spectroscopy. To obtain maximum overlap of the aromatic rings, we prepared a series of 3-hydroxynaphthalene-2-carbaldehyde derivatives. Schiff bases **6e**, **6g**, and **6h** were obtained from **5e**,[15] **5g**,[18] and **5h**,[19] respectively, after reaction with **4** in methanol. The ^{1}H NMR test responded positively, suggesting the formation of molecular assemblies of type "host–guest" between **6e**, **6g**, and **6h** and **2a**. The association constants were determined by ^{1}H NMR titration experiments and were found to be around 7 M^{-1} (Table 2, Entries 5, 7, and 8). These results confirmed the importance of the spatial arrangement of the aromatic rings and the maximization of their overlap to obtain a molecular tweezer. Moreover, we learnt, by comparing **6e** and **6g**, that the tweezer can be prepared either from an aromatic derivative bearing a 2-hydroxy carbaldehyde or a methyl ketone without any alteration of the spatial arrangement of the aromatic rings.

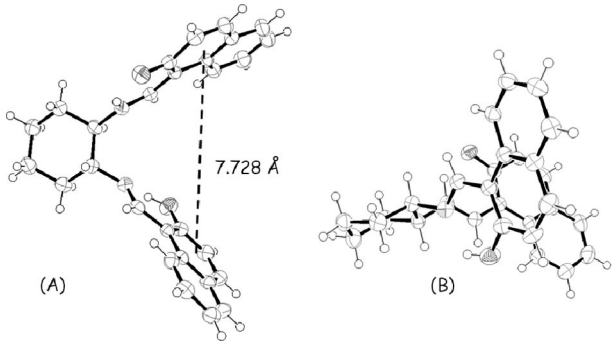


Figure 6. X-ray structure of compound **6d**.

These last results are particularly encouraging, and to reinforce these observations, 10-hydroxyphenanthrene-9-carbaldehyde (**5i**)[20] was prepared and converted into chiral tweezer **6i** after stirring with **4**. Crystals suitable for X-ray diffraction analysis were obtained. Although the X-ray structure shows that the aromatic rings are not perfectly parallel, **6i** meets the criteria for giving an efficient molecular tweezer (Figure 7). A complex **2a@6i** was obtained by mixing molecular tweezer **6i** with **2a**, and the association constant determined by ^{1}H NMR spectroscopy was 24 ± 1 M^{-1} (Table 2, Entry 9). So far, crystals of **2a@6i** suitable for X-ray diffraction analysis have not been obtained to confirm that **2a** is sandwiched between the two aromatic moieties. The same tweezer **6i** was also placed in the presence of electron-deficient NBD (**2i**) to afford molecular assembly **2i@6i** with 4 ± 1 M^{-1} ($\Delta\delta_{max} = 986 \pm 129$ Hz) as association constant at 298 K determined after ^{1}H NMR titration.

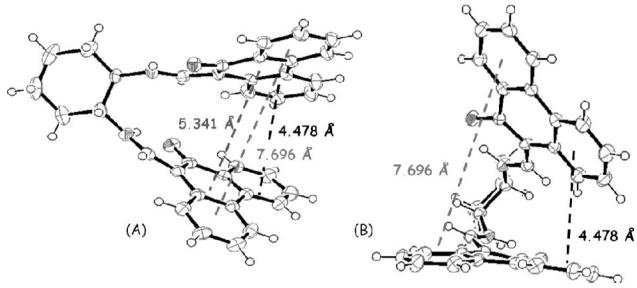


Figure 7. X-ray structure of tweezer **6i**.

Conclusions

In summary, we demonstrated that chiral molecular tweezer **1** prepared from (+)-usnic acid and (1*R*,2*R*)-1,2-diaminocyclohexane (**4**) forms host–guest complexes with a variety of aromatic compounds. The association constants of these molecular assemblies were determined by two different methods (^{1}H NMR and UV/Vis spectroscopy) and showed good correlation between the values. We then aimed to design new chiral molecular tweezers by using **4** as a spacer and various *ortho*-hydroxybenzaldehyde and aryl ketone derivatives. This work enabled us to determine the elements necessary for the formation of tweezers: (1) *ortho*-Hydroxybenzaldehyde and arylketone derivatives are required to have a stable imine function. (2) The centroid–centroid distance should be around 7–8 Å. (3) To maximize aromatic overlap, the angle formed between the planes of the two aromatic pincers should be close to 0° (in comparison, this angle is 14.2° in tweezer **1** and 4.7° in molecular assembly **3a**).

Although the association constants are low, the possibility of using functionalized guests as esters allows the use of this chiral molecular tweezer as a new tool for chiral recognition of chiral guests to be foreseen. Investigations in the field of chiral discrimination are currently in progress[21] as is the synthesis of other chiral molecular tweezers by varying either the spacer or the pincers and their use. To have an explanation of aromatic host–guest interactions with our system, electrostatic potential surfaces (EPS)[22] are underway and will be reported in due course.

Experimental Section

General Procedure for the Synthesis of Potential Tweezers: To a solution of 1,2-diaminocyclohexane in methanol (3 mL/0.5 mmol diamine) was added the carbonyl derivative (2 equiv.). The mixture was stirred at room temperature or heated to reflux until complete disappearance of the starting material was observed. The product of reaction was isolated either by filtration of the reaction mixture and crystallization (for **6c**, **6e**, **6g**, **6h**, and **6i**) or after evaporation of the solvent and purification on silica gel with CH_2Cl_2/MeOH (95:5) (for **6a**, **6b**, and **6d**).

CCDC-755089 (for **3i**), -731096 (for **6c**), -711952 (for **6d**), and -765948 (for **6i**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see also the footnote on the first page of this article): Details of the calculation of association constants. Detailed description of all experimental procedures, synthesis, and analytical data for all compounds.

Acknowledgments

Financial support by the Université de Rennes 1, the Région Bretagne, and Rennes Métropole are gratefully acknowledged.

[1] a) C. A. Hunter, K. R. Lawson, J. Perkins, C. Urch, *J. Chem. Soc. Perkin Trans. 2* **2001**, 651–669; b) E. A. Meyer, R. K. Castellano, F. Diederich, *Angew. Chem. Int. Ed.* **2003**, *42*, 1210–1250; c) A. Tewari, R. Dubey, *Bioorg. Med. Chem.* **2008**, *16*, 126–143; d) C. Bissantz, B. Kuhn, M. Stahl, *J. Med. Chem.* **2010**, *53*, 5061–5084.
[2] C.-W. Chen, H. W. Whitlock, *J. Am. Chem. Soc.* **1978**, *100*, 4921–4922.
[3] F.-G. Kläner, B. Kahlert, *Acc. Chem. Res.* **2003**, *36*, 919; M. Harmata, *Acc. Chem. Res.* **2004**, *37*, 862–873.
[4] B. Legouin, P. Uriac, S. Tomasi, L. Toupet, A. Bondon, P. van de Weghe, *Org. Lett.* **2009**, *11*, 745–748.
[5] L. Fielding, *Tetrahedron* **2000**, *56*, 6151–6170.
[6] K. A. Connors, *Binding Constants – The Measurement of Molecular Complex Stability*, Wiley, New York, **1987**.
[7] P. Job, *Ann. Chim. App.* **1928**, *9*, 113–203.
[8] A. E. Rowan, J. A. A. A. Elemans, R. J. M. Nolte, *Acc. Chem. Res.* **1999**, *32*, 995–1006.
[9] H. Benesi, H. Hildebrand, *J. Am. Chem. Soc.* **1949**, *71*, 2703–2707.
[10] B. K. Seal, A. K. Mukherjee, D. C. Mukherjee, P. G. Farrell, J. V. Westwood, *J. Magn. Res.* **1983**, *51*, 318–322.
[11] W. Person, *J. Am. Chem. Soc.* **1965**, *87*, 167–170.
[12] F. H. Stootman, D. M. Fisher, A. Rodger, J. R. Aldrich-Wright, *Analyst* **2006**, *131*, 1145–1151.
[13] F.-G. Klärner, B. Kahlert, A. Nellesen, J. Ziemau, C. Oschenfeld, T. Schrader, *J. Am. Chem. Soc.* **2006**, *128*, 4831–4841 and Supporting Information for calculations.
[14] P. G. Cozzi, *Chem. Soc. Rev.* **2004**, *33*, 410–421.
[15] K.-C. Wu, Y.-S. Lin, Y.-S. Yu, C.-Y. Chen, M. O. Ahmed, P.-T. Chou, Y.-S. Hon, *Tetrahedron* **2004**, *60*, 11861–11868.
[16] J. C. Cannadine, J. P. Corden, W. Errington, P. Moore, M. G. H. Wallbridge, *Acta Crystallogr., Sect. C* **1996**, *52*, 1014–1017.
[17] The conformational organization of the compounds obtained by X-ray (the distances between the aromatic rings, angles) does not necessarily reflect the conformation in solution; however, it can give valuable insights into the design of new tweezers.
[18] J. Einhorn, P. Demerseman, R. Royer, R. Cavier, *Eur. J. Med. Chem.* **1983**, *18*, 175–180.
[19] R. Royer, J. P. Buisson, *Eur. J. Med. Chem.* **1980**, *15*, 275–278.
[20] S. H. Alarcon, A. C. Olivieri, G. R. Guillermo, R. M. Cravero, M. Gonzalez-Sierra, *Tetrahedron* **1995**, *51*, 4619–4626.
[21] B. Legouin, M. Gayral, P. Uriac, S. Tomasi, P. van de Weghe, *Tetrahedron: Asymmetry* **2010**, *21*, 1307–1310.
[22] S. E. Wheeler, K. N. Houk, *J. Chem. Theory Comput.* **2009**, *5*, 2301–2312 and references cites therein.

Received: May 20, 2010
Published Online: August 16, 2010

