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Novel Chiral Molecular Tweezer from (+)-Usnic Acid[†]

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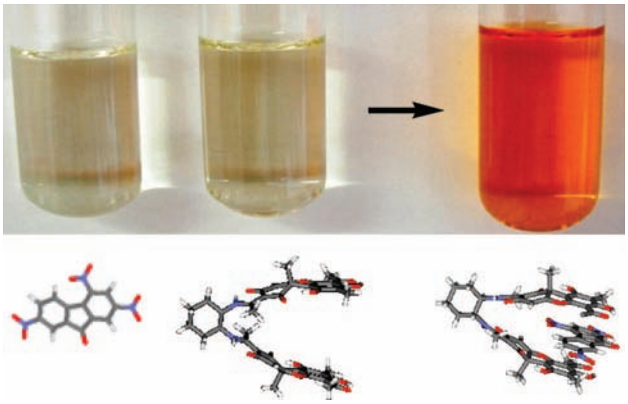
ABSTRACT



A new chiral molecular tweezer was synthesized with (1*R*,2*R*)-1,2-diaminocyclohexane as spacer and two molecules of (+)-usnic acid as pincers. The ability of this molecular tweezer to bind 2,4,7-trinitrofluorenone was studied. A charge-transfer complex was formed in which TNF was sandwiched between the two usnic acid units with $\pi-\pi$-stacked aromatic interactions.

The $\pi-\pi$-stacked aromatic interactions have been found to govern diverse molecular organizations in both solution and solid state. They not only control the vertical base−base stacking in DNA, the tertiary structures of proteins, but also play a major role in the assembly and crystallization on many natural and synthetic molecules.[1] Aromatic interactions have also been used in template-directed synthesis to control the enantioselectivity of reactions in asymmetric syntheses.[2] However, in comparison to more conventional interactions such as hydrogen bonds, ion pairs, and hydrophobic interactions, the $\pi-\pi$-stacked interaction is not well defined. To date, no commonly used model has been built to successfully interpret the experimental observations. This can be attributed to the complication of the $\pi-\pi$-stacked dependency on substituent groups, variable geometries, and the cooperative effect of various noncovalent interactions. Therefore, the study of the variety of systems involved in the $\pi-\pi$-stacked interactions is an important step toward a full understanding of this type of noncovalent interactions.

With the aim of contributing to the detailed understanding of molecular associations involving aromatic interactions,

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[†] This paper is dedicated to the memory of Dr. Christian Marazano, who passed away on November 12, 2008.

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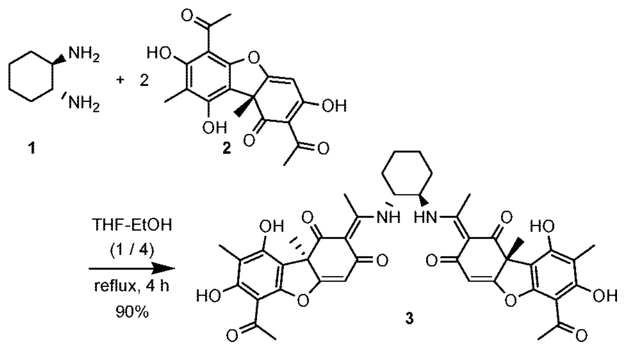
molecular tweezers[3] with a distance between the pincers of about 7 Å appear as ideal models. Herein, we describe the synthesis of a new chiral molecular tweezer in which the (1*R*,2*R*)-1,2-diaminocyclohexane **1** was used as spacer and two molecules of the abundant lichen substance (+)-usnic acid **2**[4] as complexing chromophores. On the basis of our previously reported preparation of polyamine usnic acid derivatives,[5a] **3** was synthesized as depicted in Scheme 1.

Scheme 1. Synthesis of the Molecular Tweezer **3**



After treatment of 1 equiv of diamine **1** with 2 equiv of usnic acid **2**in THF−EtOH at reflux for 4 h, compound **3** was obtained as a ketoenamine.[5] The resulting solid residue was recrystallized from ethanol to give **3** in high yield (90%).

As a continuation of our ongoing work on the use of polyamine usnic acid derivatives, we thought initially to prepare salen-type complexes by adding to **3** 1 equiv of $Ni(OAc)_2$ or $Cu(OAc)_2$. Because no complex was formed, we supposed that the usnic acid moieties do not have the same spatial disposition as the compound prepared from the ethylene diamine.[5c]

Crystals suitable for X-ray diffraction analysis were grown by slow evaporation of dichloromethane at room temperature from ethanol/dichloromethane 1:1 solution of **3**. The X-ray crystal structure analysis of **3** shows effectively that the usnic acid units are differently arranged in the space compared to the ethylene diamine derivative[5c] and that two molecules interact with each other in the solid state and that $\pi-\pi$-stacked aromatic interactions are present (Figure 1).[6] This observation lets us foresee an easy insertion of other aromatic rings between both pincers. The centroïd distances between each aromatic groups are ca. 3.7 Å. This value agrees well with those expected for $\pi-\pi$-stacking implying the occurrence of an intramolecular $\pi-\pi$ interaction in the sandwiched structure.[7] As expected the centroïd distance in **3** between aromatic rings of pincers is 7.486 Å. ^1H NMR experiments of **3** in solution of $CDCl_3$ showed a slight concentration dependence of chemical shifts indicating that **3** probably adopts a similar structure with $\pi-\pi$-stacked interactions in chloroform to that found in the crystal (see the Supporting Information).[8]

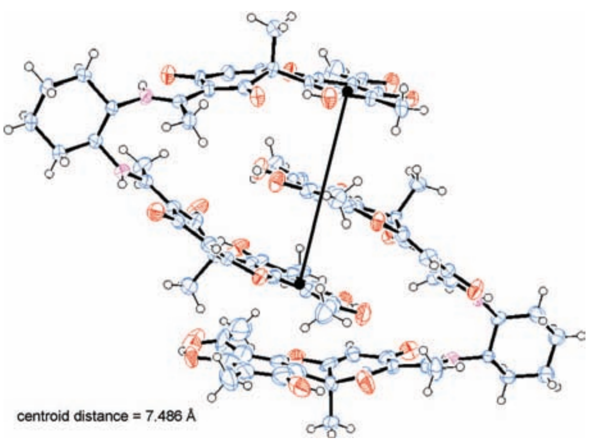
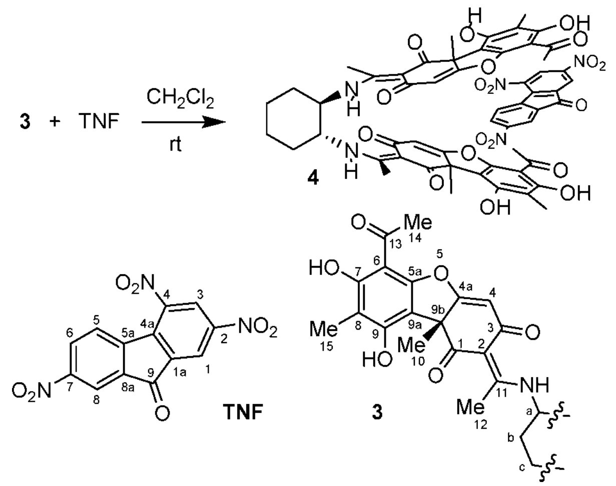


Figure 1. ORTEP drawing of the molecular structure of **3**.

The chiral molecular tweezer **3** was placed in the presence of 1 equiv of 2,4,7-trinitrofluorenone (TNF) in dichloromethane at room temperature (Scheme 2). The immediate change of color of the mixture suggests that a reaction occurred (pale yellow to red). This reaction was studied by ^1H NMR in dichloromethan-d_2 and infrared spectroscopy. The titration was followed by keeping the concentration of the guest constant (TNF). Chemical shifts of the proton of the TNF moiety, involving the most differences of chemical shifts between the substrate free and sandwiched

Scheme 2. Synthesis of the Complex **4** and Numbering Position for TNF and Molecular Tweezer **3**



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in the complex, were measured. A nonlinear least-squares treatment of $\Delta\delta_{obs} = \delta_H$ in TNF $- \delta_H$ in titration solution versus the concentration of **3** leads to a value of the association constant for the 1:1 complex **4** of 72 M^{-1} at 10 °C, according to a curve-fitting procedure described by Klärner et al.[8] Besides TNF, in solution, the force of the ligand **3** is quite similar to pheophitin and its divalent metal derivatives ($K = 30-116$ M^{-1}),[9a] lower than some acridines ($K = 150-700$ M^{-1})[9b] and much lower than bisporphyrins ($K = 410000$ M^{-1}).[9c]

Moreover, all signals corresponding to TNF in compound **4** are upfield (Figure 2). On the other hand, the vibrational frequencies observed in IR-FT for the carbonyl groups of compound **4** differ from those of compound **3** and TNF (Table 1). These results indicate the ability of the molecular tweezer to bind TNF,[10] which is probably sandwiched between the two usnic acid units.

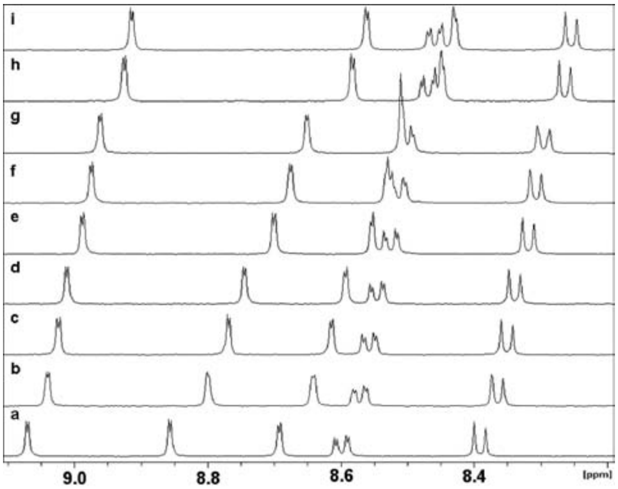

Figure 2. ^{1}H NMR spectra of the titration of TNF (1.96 mM) by **3** in CD_2Cl_2 at 500 MHz: (a) TNF; TNF + **3** at (b) 1.82 mM; (c) 3.05 mM; (d) 4.13 mM; (e) 6.21 mM; (f) 7.50 mM; (g) 8.89 mM; (h) 14.7 mM; (i) 18.17 mM.

Table 1. IR-FT Vibrational Frequencies in cm^{-1} of Carbonyl Groups in **3**, **4**, and TNF

	4	1551	
$\nu_{CO\text{-}3}$	**3**	1558	$\Delta\nu = -7$
	4	1622	
$\nu_{CO\text{-}13}$	**3**	1627	$\Delta\nu = -5$
	TNF in 4	1737	
$\nu_{CO\text{-}9}$	**TNF**	1732	$\Delta\nu = +5$

These observations were confirmed by the X-ray crystal structure analysis of the complex **4** (Figure 3). Interestingly, the crystal structure of **4** shows that two complexes interact with each other in the solid state. Those two complexes differ by the position of the TNF in the tweezer **3**. Although each TNF is sandwiched between the two usnic acid units, two different kinds of aromatic $\pi-\pi$ stacking interactions were observed. The first TNF stacks with its dinitroaromatic moiety and each aryl moiety of the adjacent usnic acids with the centroid distances A−B being 3.629 Å, B−C being 3.713 Å, and an angle of 140.04°. A supplementary weak electrostatic bond between the nitrogen atom N1 of the TNF and the oxygen atom O1 of the second complex at a distance of 3.047 Å is noted. An additional O2-centroid A contact is also observed located at the distance of 3.095 Å. This weak interaction is a classical lone pair−aromatic interaction[11] which can stabilize the crystal structure (view 1, Figure 3). The position of the second TNF in the molecular tweezer is different. The stacked interactions take place between the 5-membered ring of TNF and each aryl moiety of the pincers at centroid distances D−E of 3.930 Å and E−F being 3.768 Å and an angle of 127.35° (view 2, Figure 3). It is also very interesting to notice that the distance between both pincers (centroid distances A−C and D−F) is 6.900 Å despite of two different positions of complexation of TNF in the tweezer in the solid state. Consequently, the presence of the TNF in the tweezer dramatically reduces the distance between both usnic acid units (7.486−6.900 Å).

In order to determine the electronic nature of these aromatic interactions, we decided to use UV spectroscopy. Generally, the appearance of intense color during the reaction was associated with the formation of charge transfer complexes which absorb in the visible region. Figure 4 shows a part of the absorption spectra of the molecular tweezer **3**, the TNF, the molecular assembly **4** in dichloromethane and the calculated sum of **3** + TNF. The spectrum of **4** differs from the spectrum of the sum of **3** and TNF by a new broadband in the visible region supposing that **4** is a charge-transfer complex.[1a,12]

As a comparison, we studied the reaction between **3** and the fluorenone by NMR and by UV spectroscopy. No change of chemical shift for the aromatic proton of fluorenone, no change of color, and no appearance of a new band in the visible range were observed after mixture of both compounds. From these results, it would seem that no interaction occurs between **3** and fluorenone. The fluorenone is probably not

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(6) The molecules of water which are present in the crystals were voluntarily omitted to simplify the figure. However, it seems that their presence adds to the stability of the assembly by the existence of hydrogen bonds.

(7) (a) Tsuzuki, S.; Honda, K.; Uchimaru, T.; Mikami, M.; Tanabe, K. *J. Am. Chem. Soc.* **2002**, *124*, 104–112. (b) Sinnokrot, M. O.; Valeev, E. F.; Sherril, C. D. *J. Am. Chem. Soc.* **2002**, *124*, 10887–10893. (c) Beg, S.; Waggoner, K.; Ahmad, Y.; Watt, M.; Lewis, M. *Chem. Phys. Lett.* **2008**, *455*, 98–102.

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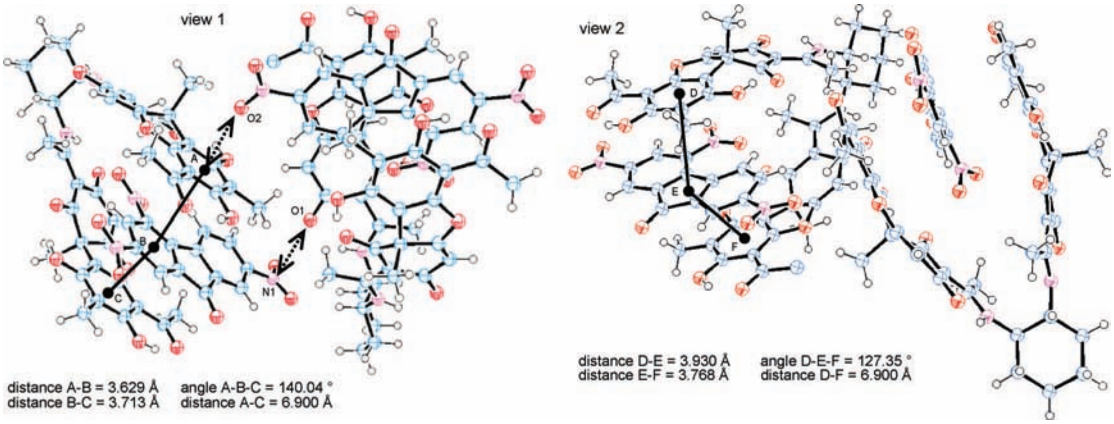

Figure 3. ORTEP drawing of the molecular structure of **4** (arbitrary atoms labeling).

electronically deficient enough to associate as charge-transfer complex with the molecular tweezer **3**.

In conclusion, we have developed a simple and efficient synthesis of a molecular tweezer in which the (1*R*,2*R*)-1,2-diaminocyclohexane **1** was used as spacer and two molecules (+)-usnic acid **2** were used as pincers. This new chiral molecular tweezer gives a charge-transfer complex in which 1 equiv of TNF is sandwiched. This tweezer seems to be a valuable model to study the nature of $\pi-\pi$-stacked aromatic interactions. Further investigations of the comprehension, the scope, and use of this chiral molecular tweezer, as well as other preparations of molecular tweezers with (+)-usnic acid as pincers, are currently in progress and will be reported in due course.

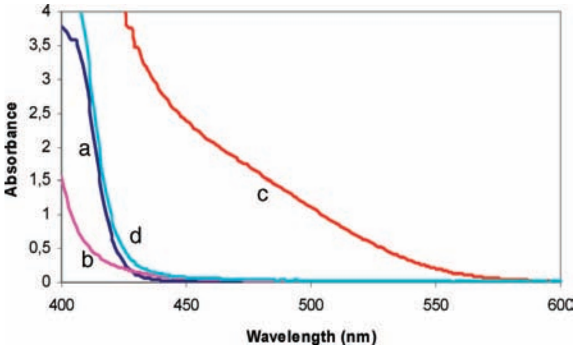

Figure 4. Absorption spectra of (a) TNF (10^{-2} M), (b) **3** (10^{-2} M), (c) the complex **4** (10^{-2} M as analytical concentration, $3.27.10^{-3}$ M once equilibrium is reached) in dichloromethane, and (d) calculated sum of **3** + TNF.

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Supporting Information Available: Details of calculations, experimental procedures, ^{1}H and ^{13}C NMR data, and CIF data of **3** and **4**. The CIF files have been deposited at the Cambridge Crystallographic Data Centre with registry nos. CCDC 705370 for **3** and CCDC 706184 for **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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