Novel Chiral Molecular Tweezer from (+)-Usnic Acid

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SUPPORTING INFORMATION

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^{1}H and ^{13}C NMR were measured on a 270 MHz Jeol and on a 500 MHz Brucker.

UV-visible spectra were recorded on a UVIKON 931 spectrophotometer from Kontron Instrument from solution at 5.10^{-2} mol.L^{-1} in chloroform.

IR FT spectra were run on FT IR 16 PC Perkin Elmer spectrometer (KBr pellets, 1%, ν cm^{-1}).

1. Calculation of association constant K

The formation of 1:1 inclusion complex of the host molecule **3** and the guest molecule TNF can be expressed as :

$$\mathbf{3} + \text{TNF} \rightleftharpoons \mathbf{4}$$

Therefore, the stoechiometric formation constant is given by :

$$K = \frac{[4]}{[3]\,[\text{TNF}]} = \frac{[4]}{([3]_0 - [4])([\text{TNF}]_0 - [4])} \quad (1)$$

where $[\mathbf{3}]_0$ and $[\text{TNF}]_0$ are the initial concentrations of the host (**3**) and the guest (TNF)

The association constant was calculated by curve fitting (with NLREG version 4.1., P.H. Sherrod, a Non Linear Regression Analysis Program) of the proton chemical shift changes at 25 °C, assuming that the chemical shift (δ_{obs}) of a proton signal of the guest molecule can be represented by the sum of fractionnal contributions from the free and complexed guest molecules:

$$\delta_{obs} = \frac{[\text{TNF}]}{[\text{TNF}] + [4]}\delta_{\text{TNF}} + \frac{[4]}{[\text{TNF}] + [4]}\delta_4 \quad (2)$$

Combination of equations (1) and (2) leads to equation (3) [1] :

$$\Delta\delta = \frac{\Delta\delta_{max}}{[\text{TNF}]}\left(\frac{1}{2}\left([3] + [\text{TNF}] + \frac{1}{K}\right) - \sqrt{\frac{1}{4}\left([3] + [\text{TNF}] + \frac{1}{K}\right)^2 - [3][\text{TNF}]} \right) \quad (3)$$

where $\Delta\delta = \delta_H$ in TNF $- \delta_H$ in titration solution, $\Delta\delta max = \delta_H$ in **TNF** $- \delta_H$ in **4**.

The titration was followed in dichloromethan at 283 K by keeping as a constant the concentration of the guest (**TNF**) while the concentration of the host (**3**) was increasing. This was achieved by dissolving compound **3** at 19.9 mM in a TNF solution at 1.96 mM and by progressively adding this solution to the one of TNF.

For the mathematical treatment, we only considered the proton H$_3$ which involved the most differences of chemical shifts between the substrate free and engaged in the complex [1].
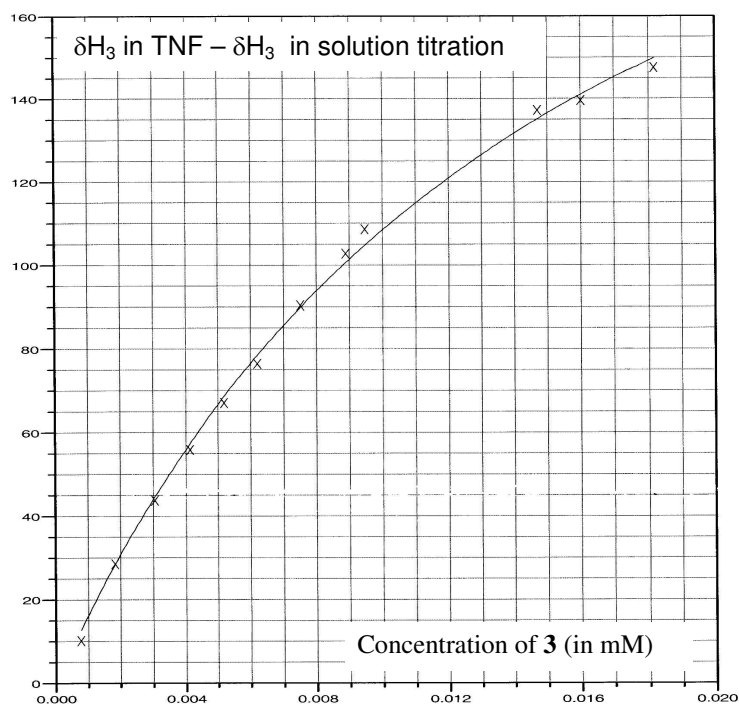
Host : **3**   Guest : **TNF**   [TNF]$_0$ = 1.96 mM

T = 10 °C   Solvent : CD$_2$Cl$_2$

δ_{H_3} in **TNF** = 8.859 ppm

[**3**] (mM)	δ_{H_3} (ppm)	$\Delta\delta_{H_3}$ (ppm)
0.77	8.839	0.020
1.82	8.802	0.057
3.05	8.772	0.087
4.13	8.748	0.111
5.19	8.725	0.134
6.21	8.706	0.153
7.50	8.679	0.180
8.89	8.654	0.205
9.47	8.642	0.217
14.70	8.585	0.274
16.00	8.580	0.279
18.17	8.564	0.295

Table S1 : ^{1}H NMR chemical shifts in CD$_2$Cl$_2$ at 10 °C at 500 MHz of titration solutions of **3** and TNF, the concentration of TNF being constant.

K = 72 M^{-1}
$\Delta\delta$max = 0.542 ppm

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2. Concentration dependance of chemical shift of 3 in chloroform solution

^{1}H NMR spectra of **3** were recorded in CDCl$_3$ at different concentrations. Chemical shifts are gathered together in Table S4.

	11.40 mg in 0.7 mL	15.79 mg in 0.7 mL	21.72 mg in 0.7 mL
m, 2H, **H**-b	1.50	1.50	1.50
s, 6H,C**H**$_3$-10	1.56	1.53	1.54
m, 2H, **H**-c	1.63	1.63	1.63
m, 8H, C**H**$_3$-15, **H**-b	2.01	2.00	1.99
m, 2H, **H**-c	2.20	2.21	2.21
s,6H, C**H**$_3$-12	2.56	2.56	2.56
s,6H,C**H**$_3$-14	2.61	2.60	2.59
s, 2H, **H**-a	3.83	3.83	3.84
s, 2H, **H**-4	5.74	5.74	5.74
s,2H, O**H**-9	11.70	11.69	11.69
s, 2H, O**H**-7	13.25	13.24	13.23
s, 2H, N**H**	13.96	13.95	13.95

Table S4 : ^{1}H chemical shifts at 270 MHz of compound **3** at different concentrations.

3. Synthesis

3.1. Synthesis of compound 3 : To a solution of usnic acid (1g, 2.90 mmol, 2 eq) in THF/EtOH (20:80) (15 mL) was added dropwise (1R,2R)-(-)-1,2-diaminocyclohexane (0.178g, 1.53mmol, 1.05 eq.). After stirring and heating to reflux at 100 °C for 4 h under argon, ethanol was added to precipitate **3**. After filtration, the solid was recrystallized with EtOH giving **3** (2 g, 90%) as a pale-yellow solid.
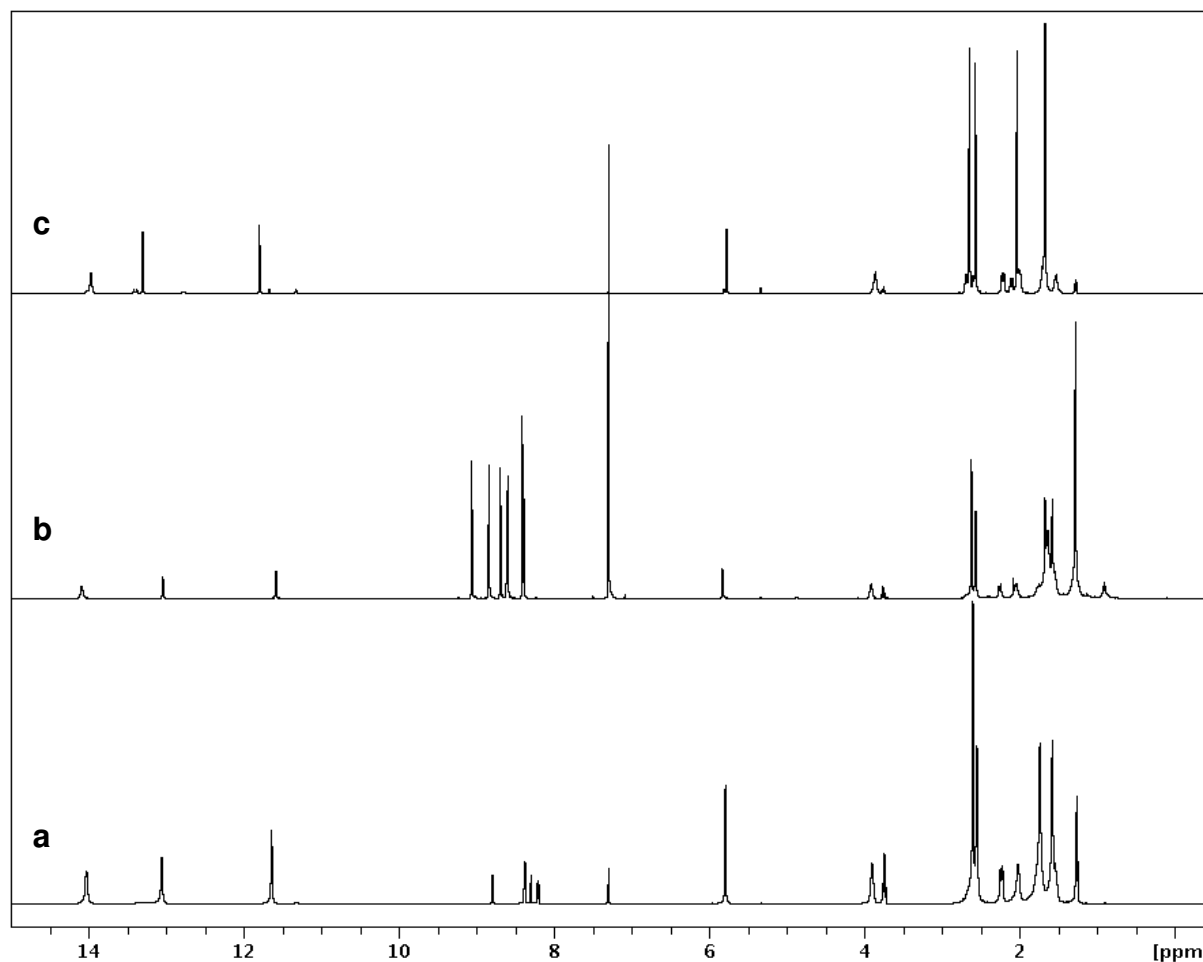
$[\alpha]_D^{20}$ = +234.5 (*c* 1, CH$_2$Cl$_2$)

^{1}H NMR (500 MHz, CDCl$_3$) δ 1.50 (m, 2H, **H**-b); 1.59 (s, 6H, C**H**$_3$-10); 1.66 (m, 2H, **H**-c); 1.96 (m, 8H, C**H**$_3$-15, **H**-b); 2.19 (m, 2H, **H**-c); 2.53 (s, 6H, C**H**$_3$-12); 2.57 (s, 6H,C**H**$_3$-14); 3.85 (s, 2H, **H**-a); 5.72 (s, 2H, **H**-4); 11.71 (s, 2H, O**H**-9); 13.11 (s, 2H, O**H**-7); 13.94 (s, 2H, N**H**); ^{13}C NMR (125 MHz, CDCl$_3$) δ 7.33 (**C**H$_3$-15); 18.19 (**C**H$_3$-12); 23.85 (**C**-b); 31.08 (**C**H$_3$-14); 31.93(**C**H$_3$-10); 32.05 (**C**-c); 57.05 (**C**-a); 57.36 (**C**-9b); 100.97 (**C**-6); 101.85 (**C**-2); 102.05 (**C**-4); 104.73 (**C**-9a); 107.79 (**C**-8); 155.47 (**C**-6a); 157.92 (**C**-9); 163.21 (**C**-7); 174.43 (**C**-11); 174.53 (**C**-4a); 191.26 (**C**-3); 198.21 (**C**-1); 200.27 (**C**-13).HRMS (CI): [M+Na]$^+$ calcd for C$_{42}$H$_{42}$N$_2$O$_{12}$Na: 789.2635; found 789.2629; IR-FT : 3200-2250 (OH, NH), 1699 (CO-1), 1627 (CO-13), 1558 (CO-3)

3.2. Synthesis of compound 4 : One equivalent of **3** in CH$_2$Cl$_2$ is added to one equivalent of TNF in CH$_2$Cl$_2$ involving an immediate change of color of the reaction mixture. Solvent is removed to give a red solid.

$[\alpha]_D^{20}$ = +190.3 (*c* 1.08, CH$_2$Cl$_2$)

Due to the low value of the constant of complexation, it is not possible to have the chemical shifts of the complex form on only a spectrum. Either we have the chemical shifts of the TNF under its complex form, **3** being free or we have the chemical shifts of the tweezer under its complex form, the ligand being free.

Spectra in CDCl$_3$ at 500 MHz at 10°C of (a) TNF under its complex form, **3** in excess; (b) **3** under its complex form, TNF in excess, (c) **3** (alone)

Chemical shifts of **4** in CDCl$_3$ once equilibrium is reached (33% of complexation from K value)

^{1}H NMR (500. MHz, CDCl$_3$) : δ 1.50 (m, 8H), 1.63 (m, 8H), 1.98 (m, 2H,), 2.18 (m, 2H, **H**-c), 2.48 (s, 6H, C**H**$_3$-12), 2.57 (s, 6H, C**H**$_3$-14), 3.86 (m, 2H, **H**-a), 5.75 (s, 2H, **H**-4), 8.21 (d, $J = 8$ Hz, 1H, **H**-5'), 8.40 (m, 2H, **H**-6' and **H**-8'), 8.49 (d, $J = 2$ Hz, 1H, **H**-3'), 8.83 (d, $J = 2$ Hz, 1H, **H**-1'), 11.50 (s, 2H), 12.95 (s, 2H), 14.01 (s, 1H), 14.02 (s, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) : δ 7.15 (**C**H$_3$-15); 18.31 (**C**H$_3$-12); 23.96 (**C**-b); 31.08 (**C**H$_3$-14); 31.78 (**C**H$_3$-10); 32.01 (**C**-c); 57.18 (**C**-a); 57.24 (**C**-9b); 100.96 (**C**-6); 101.80 (**C**-2); 102.34 (**C**-4); 104.69 (**C**-9a); 107.79 (**C**-8); 119.61 (**C**H-5'); 122.43 (**C**H-6'); 125.55 (**C**H-8'); 128.05 (**C**H-3');130.34 (**C**H-1'); 135.93 (**C**-7'); 137.99 (**C**-4'); 139.11 (**C**-2'); 143.02 (**C**-5a'); 144.44 (**C**-4a'); 148.65 (**C**-8a'); 149.84 (**C**-1a'); 155.41 (**C**-6a); 157.73 (**C**-9); 163.09 (**C**-7); 174.36 (**C**-11); 174.67 (**C**-4a); 185.45 (**C**-9'); 191.27 (**C**-3); 198.05 (**C**-1); 200.31 (**C**-13); IR-FT : 3200-2250 (OH, NH), 1737 (C=O, TNF), 1699 (CO-1), 1622 (CO-13), 1551 (CO-1).

Figures and letters indexed by an apostrophe identify carbon or proton belonging to the TNF molecule in the complex **4**.

References

(1) Klärner, F.-G.; Kahlert, B.; Boese, K.; Bläser, D.; Juris, A.; Marchioni, F. *Chem. Eur. J.* **2005**, *11*, 3363-3374.

4. ^{1}H and ^{13}C NMR Spectra