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Binding of caffeine by a synthetic co-receptor

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Abstract

A new co-receptor macrobicyclophane for binding caffeine has been developed. The co-receptor binding sites are based on the hydrogen bonding abilities of secondary amides. ^{1}H NMR titrations demonstrate recognition of caffeine by formation of a 2:1 complex in $CDCl_3$. © 2000 Elsevier Science Ltd. All rights reserved.

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In the field of supramolecular chemistry, the pursuit of preorganization[1] has led to intense interest in the construction of macropolycyclic architectures.[2] The combination of two discrete binding subunits, which may cooperate for the simultaneous complexation of two substrates within the same macropolycyclic cavity leads to ditopic co-receptor[3] molecules which also have potential as catalysts. Three-dimensional macrobicyclic receptors of the cyclophane type have been extensively used in molecular recognition studies, and starting from our previous studies on tripodal cleft-shaped receptors, we have been investigating dimerization strategies for the construction of a macrobicyclic cyclophanes with co-receptor properties (Fig. 1). Here, we report the first such molecular box which is capable of accommodating two molecules of caffeine inside a large functionalized cavity.

The molecular scaffold used for the construction of the top and bottom of the box was the tris-aryl substituted benzene **1**, previously used as a spacer in our tripodal receptors.[4] The walls of the box are based on a diphenylmethane unit, **2**, which has also been used in the construction of cyclophanes receptors.[5] These two building blocks have been combined to produce a new hybrid macrocyclophane *endo* co-receptor (Scheme 1). Condensation of the triacid chloride **1** with excess 1,1-[3,5-dimethyl-4-aminophenyl]cyclohexane **2** afforded the triamide-triamine **3** in 56% yield.[6] Macrocyclization of **3** with **1** under high dilution conditions produced the molecular box **4** in 36% yield.[7] The six propyl groups on the periphery of the macrobicyclophane are required to make it soluble in nonpolar organic solvents such as chloroform. Molecular mechanics calculations using the AMBER* force field as implemented

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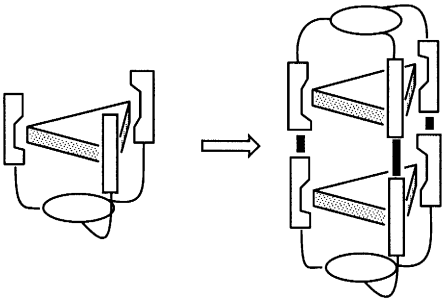
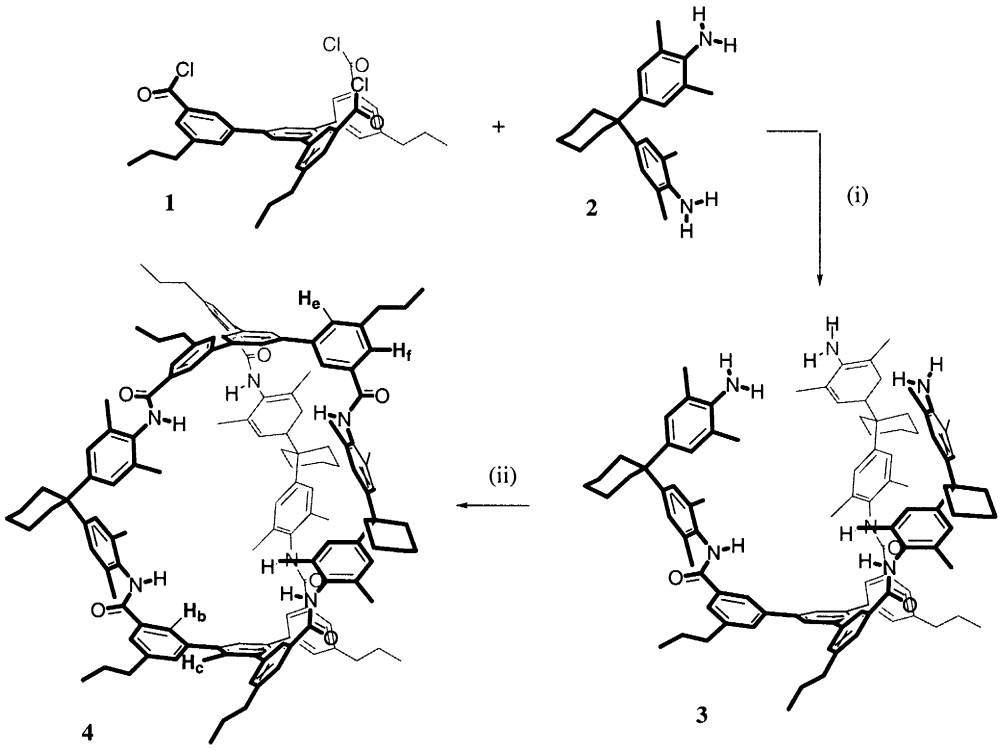


Fig. 1.

in Macromodel[8] indicate that the lowest energy conformation of the box has all six amide hydrogens directed towards the interior of the cavity. The simple NMR spectrum of the macrobicyclophane is consistent with a C_3-symmetrical structure.



Scheme 1. Reagents and conditions: (i) CH_2Cl_2/Et_3N, room temperature, 24 h, 56%; (ii) high dilution conditions: 1,3,5-tris(3′-chloroformyl-5′-propylphenyl) benzene CH_2Cl_2/triethylamine, room temperature, 7 days, 36%

We therefore have a box with two identical binding sites each armed with three convergent amide N–Hs which will be complementary to triple hydrogen bond acceptor molecules of appropriate shape and size. Models suggested that xanthine derivatives fulfil the requirements.

The binding of macrobicyclophane **4** to xanthine derivatives **5** (caffeine) and **6** was monitored by ^{1}H NMR titrations in $CDCl_3$. Addition of **5** or **6** to solution of **4** produced a significant upfield shift in the signal due to the amide protons indicating formation of a hydrogen-bonded complex.

A Job plot[9]gave a maximum at a **4**:**5** ratio of 0.6 which is indicative of a 2:1 stoichiometry.[10] The NMR titration data, following the upfield shift of the **4** amide signal, for the complexes containing **5**

and **6** were analyzed with curve fitting software using 1:1 and 2:1 complexation models. The fit was convincingly better for the 2:1 complexation stoichiometric model than for any other model (Table 1). The values of the microscopic association constants[11] and the complexation-induced changes in chemical shift for the two binding events are very similar, which shows that there are two identical binding sites with negligible cooperation between them. Compound **4** binds to the xanthine derivatives **5** and **6** with a modest affinity to form 2:1 complexes (K_a (**4**+**5**⇔**4**·**5**$_2$)=7050±56 M^{-2} and K_a (**4**+**6**⇔**4**·**6**$_2$)=2632±24 M^{-2}). To confirm the 2:1 stoichiometry, we prepared the caffeine dimer **7** and studied complexation with host **4** using isotermal titration calorimetry (ITC)[12] in $CHCl_3$ at 298 K (Fig. 2). Complexation of **7** is exothermic ($\Delta H = -7.4$ kcal mol^{-1}), K_a=923[13]±7 M^{-1}, and the stoichiometry (*n*), which was determined as an independent parameter in the data analysis, is 0.932±0.03.[13] In other words, host **4** and dimer **7** form a 1:1 complex with a significant increase in association constant, compared with **4**·**5** or **4**·**6**. The simplest explanation is that each caffeine unit of **7** interacts with one of the binding sites of **4**, leading to a cooperative ditopic interaction with the co-receptor.

Table 1
Microscopic (statistically corrected) association constants and complexation-induced changes in chemical shift for ^{1}H NMR titrations in $CDCl_3$ at 298 K

Equilibrium	$K_{1m}(M^{-1})$	$K_{2m}(M^{-1})$	$\Delta\delta_{NH}$	$\Delta\delta_{Me(1)}$	$\Delta\delta_{Me(3)}$	$\Delta\delta_{Me(7)/CH2\ Ph}$
4 + **5** ⇔ 4•**5**	94 ± 8		+0.89	-0.41	-0.44	-0.66
4•**5** + **5** ⇔ 4•**5**$_2$		75 ± 7	+0.90[a]	-0.49	-0.45	-0.72
4 + **6** ⇔ 4•**6**	56 ± 4		+0.80	-0.46	-0.46	-0.62
4•**6** + **6** ⇔ 4•**6**$_2$		47 ± 3	+0.90[a]	-0.31	-0.35	-0.48

[a] This is the difference between the chemical shift of the 1:1 complex and the 2:1 complex, i.e. the change in chemical shift for the 2:1 complex relative to the free receptor is approximately +1.8 ppm.

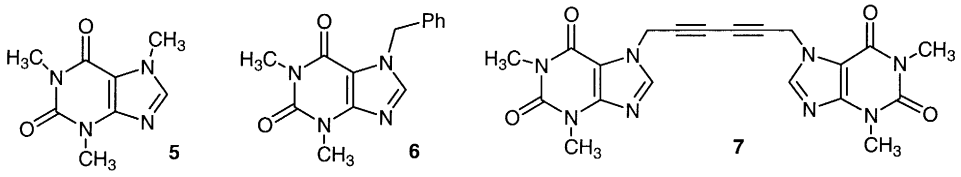


Fig. 2. Structures of xanthine derivatives

The geometry of the **4**·**5**$_2$ complex was investigated using a 2D ROESY experiment (mixing time=0.75 s, spinlock=2 kHz, 10 mM **4**, 400 mM **5**) which revealed close intermolecular contacts between the methyl groups of the caffeine and the aromatic and amide protons of **4** (see Fig. 3). These NOEs are in good agreement with endocavity binding of the caffeine, in a geometry which places it parallel to the central benzene ring of the spacer and within stacking distance, as shown in Fig. 3B. This structure is also consistent with the large upfield changes in chemical shifts observed for the signals due to the caffeine methyl groups. The models of the free and bound forms of **4** suggest that there is no significant change in the conformation of the host on complexation. The two bound caffeine molecules are approximately 7.5 Å apart in the complex which explains the almost negligible negative binding cooperativity observed.

The binding selectivity of macrocyclophane **4** and its application to catalysis are the subjects of our current studies which will be reported on due course.

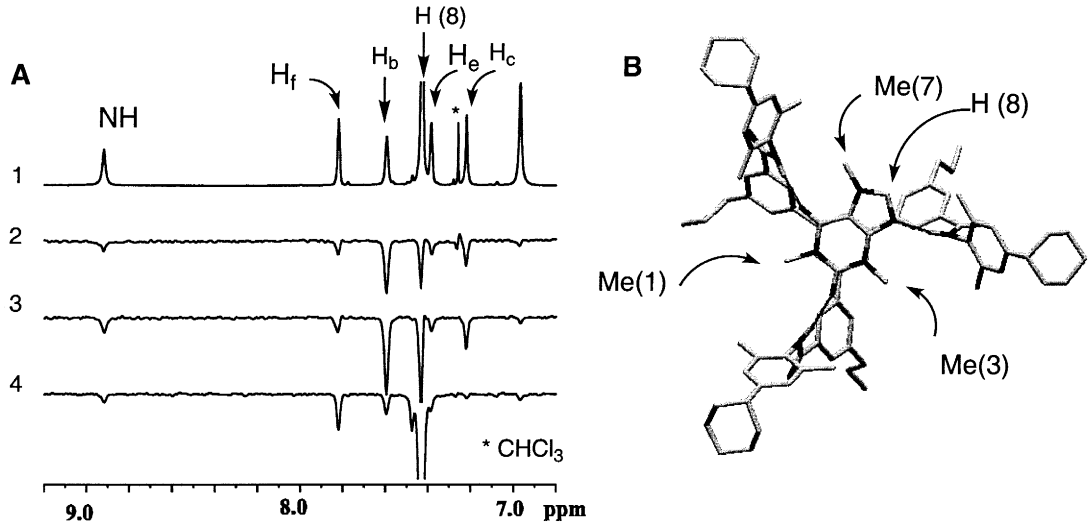


Fig. 3. (A) Region of the 1D and of selected traces of the 2D ROESY spectra; (B) top view of the proposed geometry for one binding site in the 1:2 complex $\mathbf{4}\cdot\mathbf{5}_2$. The hydrogens have been suppressed for clarity. A1=Aromatic region of the ^{1}H NMR spectrum of the 1:2 complex $\mathbf{4}\cdot\mathbf{5}_2$; A2, A3 and A4 corresponding traces of the 2D ROESY spectrum obtained at the chemical shifts of Me(1), Me(3) and Me(7), respectively. The negative peaks indicate space proximity of the related protons

Acknowledgements

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References

1. (a) Lehn, J. M. *Supramolecular Chemistry, Concepts and Perspectives*; VCH: Weinheim, 1995. (b) Lehn, J. M. *Angew. Chem., Int. Ed. Engl*. **1988**, *27*, 89. (c) Still, W. C. *Acc. Chem. Res*. **1996**, *29*, 155. (d) Metzger, A.; Lynch, V. M.; Anslyn, E. V. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 862. (e) Eblinger, F.; Schneider, H.-J. *Angew. Chem., Int. Ed. Engl*. **1998**, *37*, 826. (f) Cram, D. J. *Angew. Chem., Int. Ed. Engl*. **1986**, *25*, 1039.
2. Atwood, J. L.; Eric, J.; Davies, D.; MacNicol, D. D.; Vögtle, F.; Lehn, J. M. *Comprehensive Supramolecular Chemistry*; Pergamon Press: Oxford, 1996.
3. Kotzyba-Hibert, F.; Lehn, J. M.; Vierling, P. *Tetrahedron Lett.* **1980**, *21*, 941.
4. (a) Ballester, P.; Costa, A.; Deyà, P. M.; González, J. F.; Rotger, M. C.; Deslongchamps, G. *Tetrahedron Lett*. **1994**, *35*, 3813. (b) Ballester, P.; Costa, A.; Deyà, P. M.; Vega, M.; Morey, J.; Deslongchamps, G. *Tetrahedron. Lett*. **1999**, *40*, 171.
5. (a) Ottens-Hildebrandt, S.; Nieger, M.; Rissanen, K.; Rouvinen, J.; Meier, S.; Harder, G.; Vögtle, F. *J. Chem. Soc., Chem. Commun*. **1995**, 777. (b) Adams, H.; Carver, F. J.; Hunter, C. A. *J. Chem. Soc., Chem. Commun*. **1995**, 809. (c) Hunter, C. A. *J. Am. Chem. Soc*. **1992**, *114*, 5303.
6. Triamine-triamide, compound **3**: white solid, mp=270°C. ^{1}H NMR ($CDCl_3$) δ: 8.01 (s, 3H), 7.83 (s, 3H), 7.71 (s, 3H), 7.67 (s, 3H), 7.34 (s, 3H), 7.01 (s, 6H), 6.85 (s, 6H), 3.46 (m, 6H), 2.76 (t, J=7.32 Hz, 6H), 2.25 (s, 18H), 2.21 (m, 12H), 2.15 (s, 18H), 1.75 (m, J=7.32 Hz, 6H), 1.57 (m, 12H), 1.50 (m, 6H), 1.00 (t, J=7.26 Hz, 9H) ppm. ^{13}C NMR ($CDCl_3$) δ: 166.8, 149.2, 144.9, 142.7, 142.2, 140.8, 138.5, 136.2, 135.4, 131.7, 131.6, 127.8, 127.1, 126.5, 124.5, 122.1, 45.7, 38.7, 37.9, 27.2, 25.3, 23.7, 19.6, 18.7, 14.6 ppm. FTIR (KBr): 3600–3100, 1656, 1591, 1493, 1453, 1306, 1241, 871, 760, 702, 655 cm^{-1}. MS (*m/z*) FAB (+) 1478 (MH^+, 100%). $C_{102}H_{120}N_6O_3$ requires M^+=1477.
7. Macrobicyclophane, compound **4**: **3**, 100 mg, and 0.28 ml of triethylamine were dissolved in 45 mL of dry dichloromethane and transferred to a dropping syringe pump. Triacid chloride **1**, 42 mg was similarly dissolved in 45 mL of dry dichloromethane and transferred to an identical dropping syringe pump. These two solutions were added dropwise (0.5 mL/min) to 300 mL of dry dichloromethane with stirring under argon. The reaction mixture was then stirred for 7 days.

The dichloromethane was washed with 5% HCl, 5% $NaHCO_3$, and water, and then dried (Na_2SO_4). The solvent was evaporated under reduced pressure. The product was chromatographed on silica with chloroform:ethyl acetate (98:2) to afford macrobicyclophane **4** (49 mg, 36%) as a white solid. It was recrystallized from dichloromethane–ethanol, mp >300°C. ^{1}H NMR ($CDCl_3$) δ: 7.77 (s, 6H), 7.73 (s, 6H), 7.61 (s, 6H),7.56 (s, 6H), 7.21 (s, 6H), 6.94 (s, 12H), 2.74 (t, J=7.1 Hz, 12H), 2.21 (m, 12H), 2.17 (s, 36H), 1.74 (m, 12H), 1.59 (m, 12H), 1.56 (m, 6H), 0.99 (t, 7.3 Hz, 18H) ppm. ^{13}C NMR ($CDCl_3$) δ: 166.6, 148.3, 145, 143.4, 142.8, 136, 135.5, 131.9,131.7, 127.7, 127.6, 127.3, 124.5, 46, 38.6, 37.5, 31.6, 25.2, 23.6, 19.6, 14.6 ppm. FTIR (KBr): 3750–3100, 2950, 2850, 1650, 1600, 1500, 1410, 1350, 1250, 860 cm^{-1}. MS (*m/z*) FAB (+) 1989 (MH^+, 100%). $C_{138}H_{150}N_6O_6$ requires M^+=1988.

8. Macromodel 6.0, Department of Chemistry, Columbia University: New York, NY 10027, 1997.
9. (a) Job, P. *Ann. Chim. (Paris)* **1928**, *9*, 113. (b) Connors, K. A. *Binding Constant*; John Wiley & Sons: New York, 1987.
10. One might expect a theoretical maximum x_{max}=0.67 in the Job plot for a 2:1 complex. However, the experimental value for x_{max} depends on the product $\beta_{12}c_f$ (β_{12}=$K_{11}K_{12}$, and c_f a constant related to the sample's concentration, see Ref. 9b, page 26); the larger this quantity, the closer x_{max} will be to the theoretical limit. Generally, a deviation away from 0.5 can be taken for evidence of higher order complexes, since unless the experiment is carried out in the tight binding limit, the theoretical maximum is not achieved. Bisson, A. P.; Hunter, C. A.; Morales, J. C.; Young, K. *Chem. Eur. J.* **1998**, *4*, 845.
11. ^{1}H NMR dilution experiments show that **3**, **4**, **5** and **6** do not dimerize to any significant extent in chloroform solution (K <5 M^{-1}).
12. Wadsö, I. *Chem. Soc. Rev.* **1997**, 79. (b) Ladbury, J. E.; Chowdry, B. Z. *Chem. Biol.* **1996**, *3*, 791.
13. The obtained K_a is probably lower than might be expected for a chelate, but molecular modelling using the MMFF force field implemented in Macromodel reveals that the **4**·**7** complex is very strained, and that only five hydrogen bonds are established.