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Synthesis and supramolecular structures of molecular clips

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Abstract—The syntheses of the novel dimethylene-bridged clips **4a–e** and **5b** are reported. They selectively bind electron-deficient neutral and cationic aromatic substrates comparable to the tetramethylene-bridged tweezers **1** and **2**. The geometry of the noncovalently bound complexes with **4b–d** as receptors derived from the single-crystal structure analyses is, however, different from that of the complexes with **2** as receptor. In clip complexes the plane of the included aromatic substrate molecule is orientated almost parallel to the naphthalene side-walls of the clip, whereas in the tweezer complex the substrate is orientated parallel to the central arene spacer-unit. TCNB **19** as substrate is placed inside the cavity of the hydroquinone clip **4c** in solution as well as in the cocrystal. In contrast it was found for the cocrystal with the diacetate clip **4b** that the TCNB **19**, is placed between the naphthalene side-wall of two different clip molecules whereas in solution **19** is included into the cavity of **4b**. Finally, **19** forms a (1:2) complex with dinaphthonorbornadiene **20** in solution as well as in the crystalline state. The findings reported here are instructive for the understanding of the weak noncovalent binding forces particularly the arene–arene interaction.

1. Introduction

The processes of molecular recognition and self-assembly are of central importance in many areas of biological and supramolecular chemistry, e.g. in enzyme–substrate binding or antigen–antibody recognition as well as in the design of new materials by molecular self-assembly.[1] Both processes depend on specific, mostly noncovalent receptor–substrate interactions. Besides the relatively strong and therefore often dominating hydrogen bonding,[2] ion-pairing,[3] and the hydrophobic effects in aqueous media,[4] the noncovalent interactions of arenes with other aromatic units ($\pi-\pi$ or arene–arene interaction)[5] or with positively charged ions (cation–π interaction)[6] seem to be particularly important for the formation of supramolecules. The design of efficient synthetic receptors with the ability of selective substrate binding requires precise control of their topological and electronic properties. Besides the frequently used cyclic and, hence, well preorganized receptors of the cyclophane-type[7], noncyclic receptors with cavities of flexible size proved to be effective.[8] Recently, we have described the synthesis of the benzene- and naphthalene-spaced receptors **1** and **2**[9] which belong to a family of molecules termed molecular tweezers due to their concave–convex topology and propensity to selectively form complexes with electron-deficient aromatic and aliphatic substrates as well as organic cations via a clipping mechanism whereas electron-rich arenes or anions are not bound by **1** or **2**. This high selectivity has been correlated with markedly negative molecular electrostatic potentials (MEPs) calculated for the concave sides of **1** and **2** by using semi-empirical and quantum chemical methods.[10] When analogous calculations were performed for the electron-deficient substrates, the complementary nature of their electrostatic potentials to those inside the cavity of **1** or **2** became evident suggesting the relatively strong receptor–substrate binding to be predominantly of electrostatic nature. In order to investigate the effect of the receptor topology on the substrate specifity the number of methylene bridges shall be reduced from four in the molecular tweezers **1** and **2** to three in **3**[11] and two in **4** and **5**. We call the new receptor molecules **3**, **4**, and **5** *molecular clips* because they form complexes by clipping the substrates between their two side arms. From the calculation of electrostatic potential surfaces (EPSs, Scheme 1) we expect the trimethylene- and dimethylene-bridged clips **3–5** to selectively bind electron-deficient substrates comparable to the tetramethylene-bridged tweezers **1** and **2**. But due to their more open cavities the clips **3–5** are expected to be less specific to the shape and size of the substrate than **1** and **2**. Here we report the synthesis of the dimethylene-bridged clips **4** and **5** and their binding properties towards various neutral and cationic aromatic substrates preferentially in the crystalline state. The receptor properties of **5** and **4** in solution will be discussed elsewhere.[12]

Keywords: molecular clips; synthesis; supramolecular chemistry; single-crystal structure; analysis.
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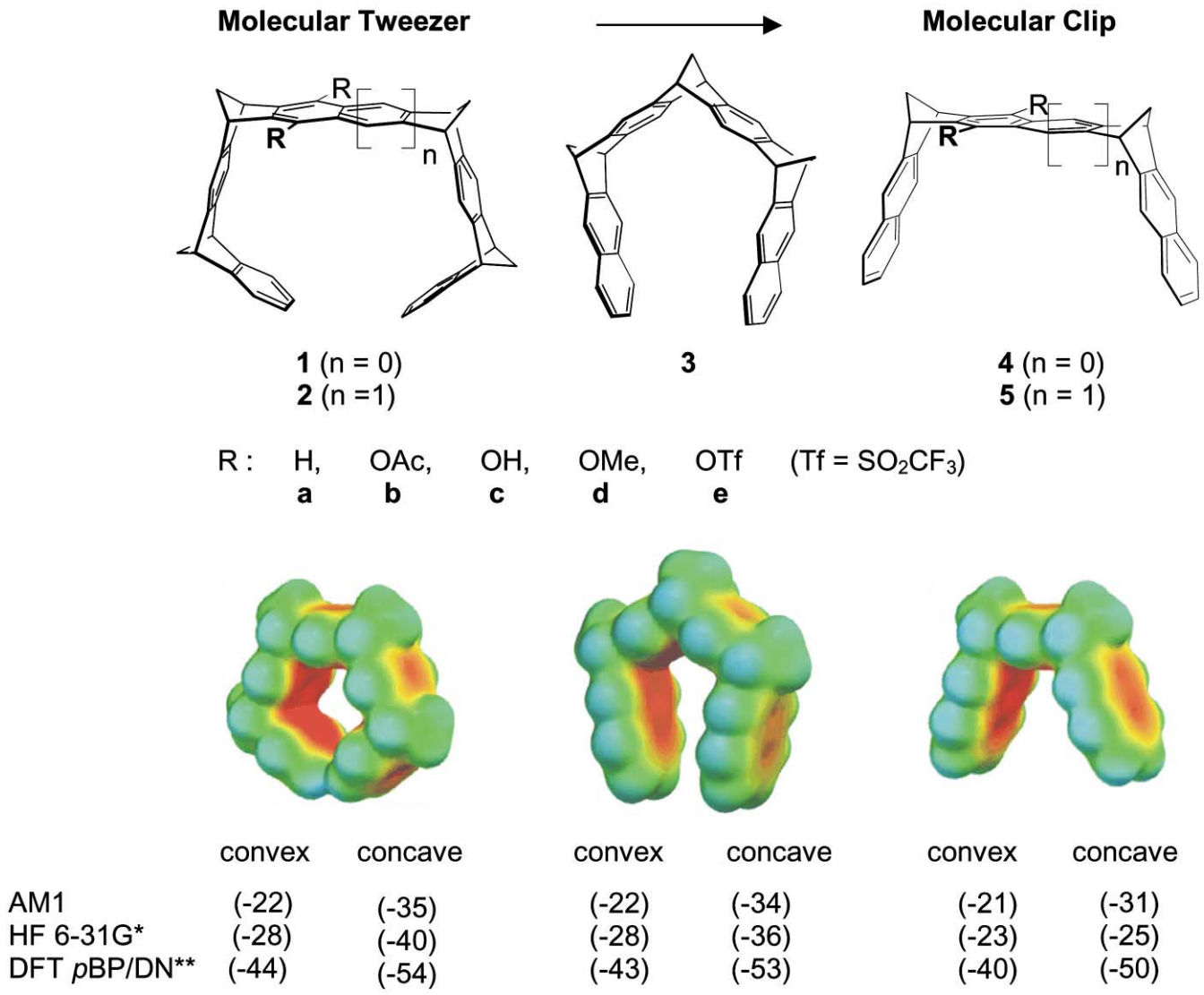
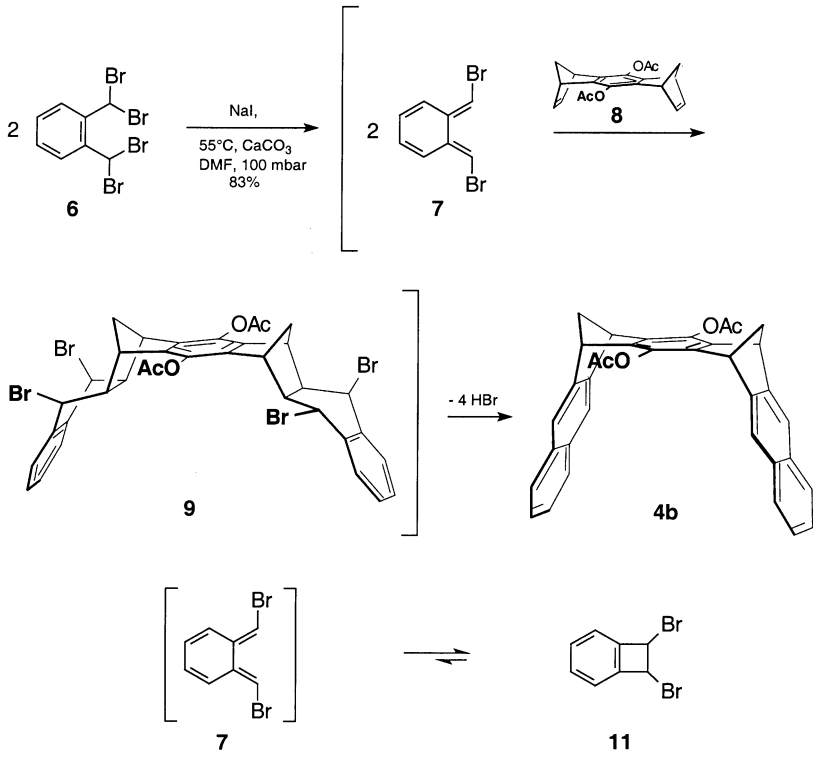


Scheme 1. Structures and EPSs of molecular tweezers and clips calculated by AM1 are depicted. The color code spans from −25 (red) to +25 kcal mol^{-1} (blue). The most negative MEPs in kcal mol^{-1} on the concave and convex side of the parent molecular tweezer **1a** and clips **3a**, **4a** calculated with semi-empirical AM1, ab initio HF/6-31G*, and DFT pBP/DN** are given in parenthesis.

2. Synthesis of the dimethylene-bridged clips 4a–e and 5b

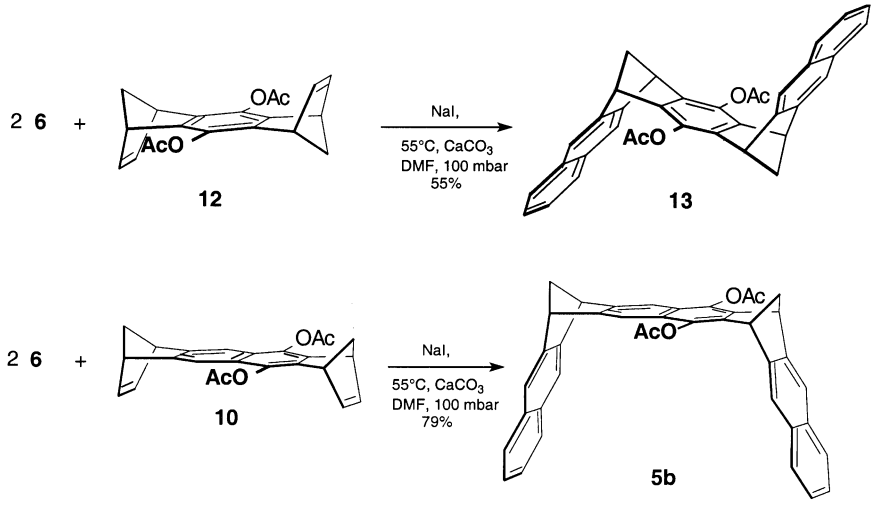
First, we tried to synthesize the clip molecule **4b** via repetitive Diels–Alder cycloadditions of *o*-quinodimethane (generated in situ by thermolysis of benzocyclobutene at 200°C)[13] to the bisdienophile **8**[14] followed by oxidative DDQ aromatization of the tetralene-units in the primary (2:1) Diels–Alder cycloadduct (DDQ—2,3-dichloro-5,6-dicyano-1,4-benzoquinone). The (2:1) Diels–Alder adduct could be isolated in almost quantitative yield, but the DDQ oxidation, tried under various conditions, failed up to date, only decomposition of the starting material has been observed. The successful synthesis of **4b** starts with the in situ generation of dibromo-*o*-quinodimethane **7** by 1,4-Br_2 elimination from tetrabromo-*o*-xylene **6** with sodium iodide as nucleophile. This reaction has been already described by Cava and Shirley in 1960.[15] In the absence of a trapping reagent **7** formed as an intermediate undergoes an electrocyclic ring-closure leading to dibromobenzocyclobutene **11**, which can be also used as a precursor of **7** at high temperature (150°C). In the presence of a dienophile such as maleic anhydride or *N*-phenyl maleic imide **7** reacts with these trapping reagents leading to the corresponding naphthalene derivatives after double HBr elimination under the conditions of reaction. Later in 1986 Paddon-Row and Patney[16] used this method to annelate naphthalene-units to norbornene and norbornadiene systems. In our first experiments using the conditions (65°C, NaI, DMF) reported by Cava[15] and Paddon-Row[16] for the reaction of **6** with **8** only 5% of the desired product **4b** could be isolated from a brownish-black oil. We assume that the reaction of the acetate functions in the product **4b** and the dienophile **8** with the hydrogen bromide generated during the reaction leads to a decomposition of **4b** and **8**, respectively. The yield of **4b** could be improved to 63% by the addition of an excess of triethylamine which binds the HBr as triethylammonium bromide. **4b** Can now be synthesized in 83% yield under the optimized conditions given in Scheme 2 and Section 5 which, however, have to be carefully controlled. At higher



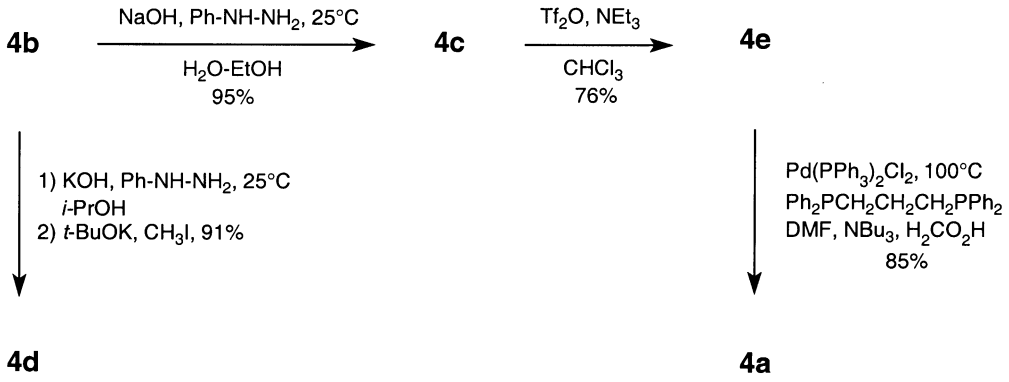
Scheme 2. Synthesis of the naphthalene, benzene-spaced clip **4b**, electrocyclic ring-closure of dibromo-*o*-quinodimethane **7**.

temperature and pressure a substantial amount of *anti*-configurated product **13** (up to 50%) is formed presumably by HBr-catalyzed rearrangement of one of the benzonorbornadiene-units either in the bisdienophile **8** (leading to **12**) or the (1:1) Diels–Alder adduct between **7** and **8** after HBr elimination. **13** can be also prepared by the reaction of **6** with the *anti*-configurated bisdienophile **12** in 55% yield. The synthesis of the naphthalene naphthalene-spaced clip **5b** (yield: 79%) proceeds analogously to that of **4b** starting from **6** and the bisdienophile **10**[14] (Scheme 3).

The clip derivatives **4a**, **4c–e** can be synthesized starting from **4b** (Scheme 4). Basic hydrolysis of the diacetate **4b** leads to the hydroquinone clip **4c**. The addition of phenylhydrazine prevents the air oxidation of **4c** to the corresponding quinone clip which smoothly occurs under the basic conditions in the absence of phenylhydrazine.[12] The parent hydrocarbon clip **4a** can be obtained by the esterification of the hydroquinone **4c** to the ditriflate **4e** with trifluoromethanesulfonic anhydride followed by the Pd-catalyzed reduction of **4e** with formic acid.[17] In the synthesis of the dimethoxy derivative **4d** it is not necessary to isolate the hydroquinone **4c** after the hydrolysis of **4b**. The methylation of **4c** was performed by addition of methyl iodide and potassium *tert*-butoxide to the mixture of hydrolysis. The structures of all new compounds were assigned by their spectroscopic data given in the experimental section and



Scheme 3. Synthesis of the *anti*-configurated compound **13** and the naphthalene, naphthalene-spaced clip **5b**.



Scheme 4. Transformation of the diacetate clip **4b** to the hydroquinone clip **4c**, the dimethoxy-clip **4d**, and the parent hydrocarbon clip **4a**.

the single-crystal structure analyses discussed in the following paragraph.

3. Single-crystal structures of 4b, 13 and of supramolecules with the clips 4b, 4c, and 4d as receptors

Crystallization of **4b** from a mixture of ethanol and dichloromethane in the presence of pyrazine gave **4b** as colorless plates suitable for a single-crystal structure analysis shown in Fig. 1. The crystal packing is characterized by introducing one methyl group of each molecule into the neighboring cavity, thus expanding the clip by 1.4 Å compared to the empty clip **4b** observed in the cocrystals of **4b** and 1,2,4,5-tetracyanobenzene (TCNB) **19** (Fig. 7) and calculated by semi-empirical AM1 and DFT pBP/DN* (vide infra). This demonstrates that in this system the methyl group has a repulsive effect in contrast to the arenes mentioned below.

13 Was obtained in two pseudopolymorphic crystalline forms from recrystallization in acetonitrile, one containing solvent molecules in the crystal lattice, and the other one solvent-free. Fig. 2 shows that the molecules of **13** are densely packed in both crystal lattices employing intermolecular slipped face-to-face interactions between the naphthalene-units and CH–π interactions between the CH_2-bridge hydrogen atoms of one clip and the naphthalene-unit of another clip.

In solution the dimethylene-bridged clip molecules **4** and **5** function as receptors comparable to the tetramethylene-bridged tweezers **1** and **2**. However, the clips generally form weaker complexes with aromatic substrates than the tweezers.[9,12] Exceptions are larger substrates such as 2,4-dinitrophenylhydrazine (**14**), 2,4-dinitrofluorobenzene (**15**), or 10,10-dicyano-2,4,7-trinitrofluorenylidene (**16**) which, for example, bind to the clip **4b** and **4c**, respectively, in chloroform with an significant association constant (K_a=28 (**14** @ **4b**), 30 (**15** @ **4b**), and 46 M^{-1} (**16** @ **4c**), 21°C) but do not show any association to the tweezer molecules **1** and **2** within the limits of ^{1}H NMR detection (Scheme 5).

The single-crystal structure analyses of the complexes between **4b**, **4c**, and **4d** as receptors and *p*-dinitrobenzene **17**, *N*-ethyl-4-carbethoxypyridinium triiodide **18**, and tetracyanobenzene **19** as substrates provide an explanation to the question, why the clip molecules **4** are less efficient receptors than the tweezer molecules **1** and **2**. The

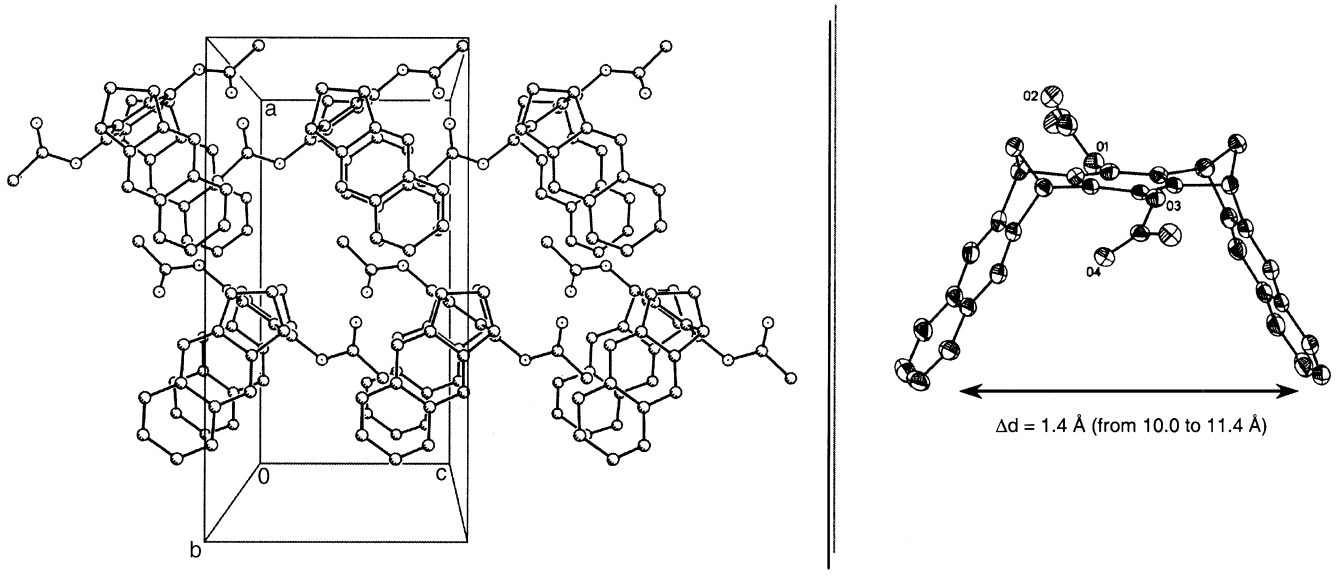


Figure 1. Single-crystal structure analysis of **4b**.

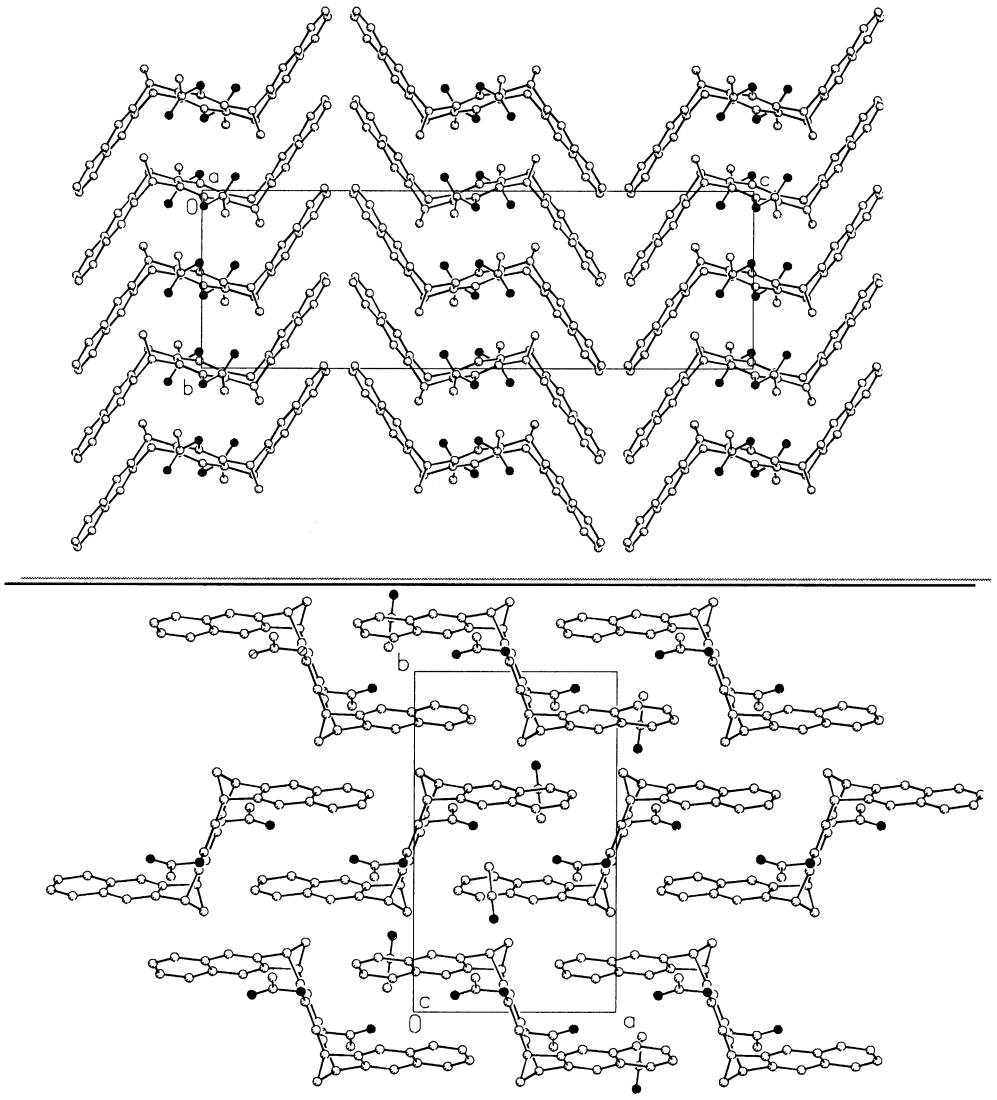
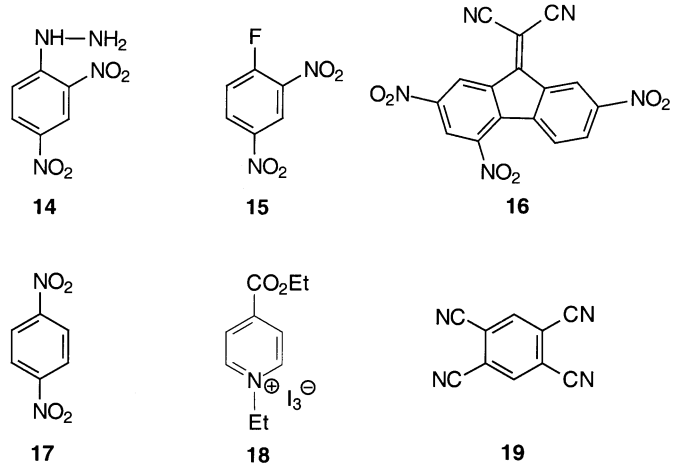


Figure 2. Single-crystal structure analysis of **13**. Solvent-free crystal (top); the crystal contains **13** and CH_3CN in a (1:2) ratio (bottom). Every second line corresponds to a different level in both crystals.



Scheme 5. Substrates noncovalently bound to the clip molecules **4b** and **4c**, respectively.

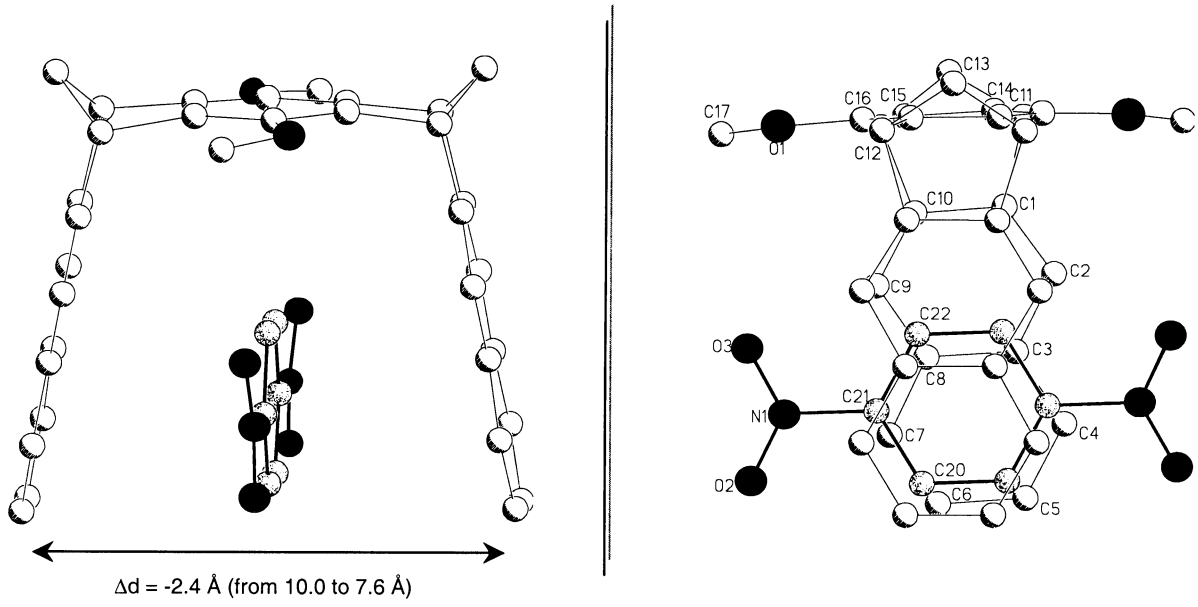


Figure 3. Single-crystal structure analysis of cocrystals containing complex **17** @ **4d** and ethanol (not shown) in a (1:2) ratio.

single-crystal structure of cocrystals containing the complex **17** @ **4d** and ethanol in a (1:2) ratio obtained from the crystallization of **17** and **4d** from ethanol/dichloromethane shows that the substrate molecule **17** is placed inside the cavity of **4d** with its plane of molecule almost parallel to the naphthalene side-walls of the receptor contrary to the geometry of the hitherto known complexes of the tweezer **2** as receptor where the plane of the substrate molecule is arranged parallel to the central naphthalene spacer-unit.[9] In order to gain attractive noncovalent substrate–receptor interactions the distance between the naphthalene side-walls, apparently, have to be compressed from about 10.0 Å in the empty receptor to 7.6 Å in the complex **17** @ **4d** (Fig. 3). The increase in steric strain resulting from this compression certainly leads to a weakening of the supramolecular complex. This conclusion is also supported by the single-crystal structure of the solvent-free complex **17** @ **4d** obtained by keeping the cocrystals in a mixture of ethanol and dichloromethane in a sealed flask for a longer period of time (about 1.5 years). **17** @ **4d** has a remarkably packing containing four complexes in the asymmetric unit with a slightly different arrangement of the substrate **17** inside the cavity of **4d** in each complex (Fig. 4). All of them obviously correspond to different enthalpies, slightly above the global minimum, thus paying for a higher packing density (Fig. 4).

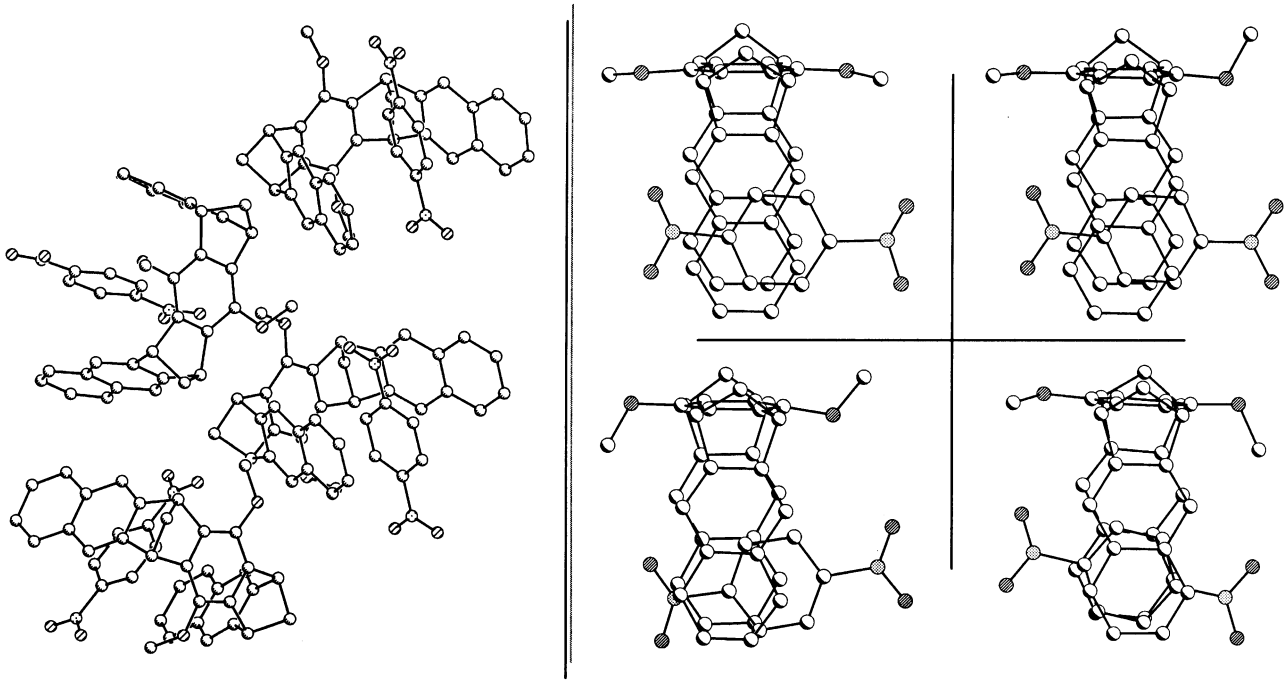


Figure 4. Single-crystal structure analysis of solvent-free complex **17** @ **4d**.

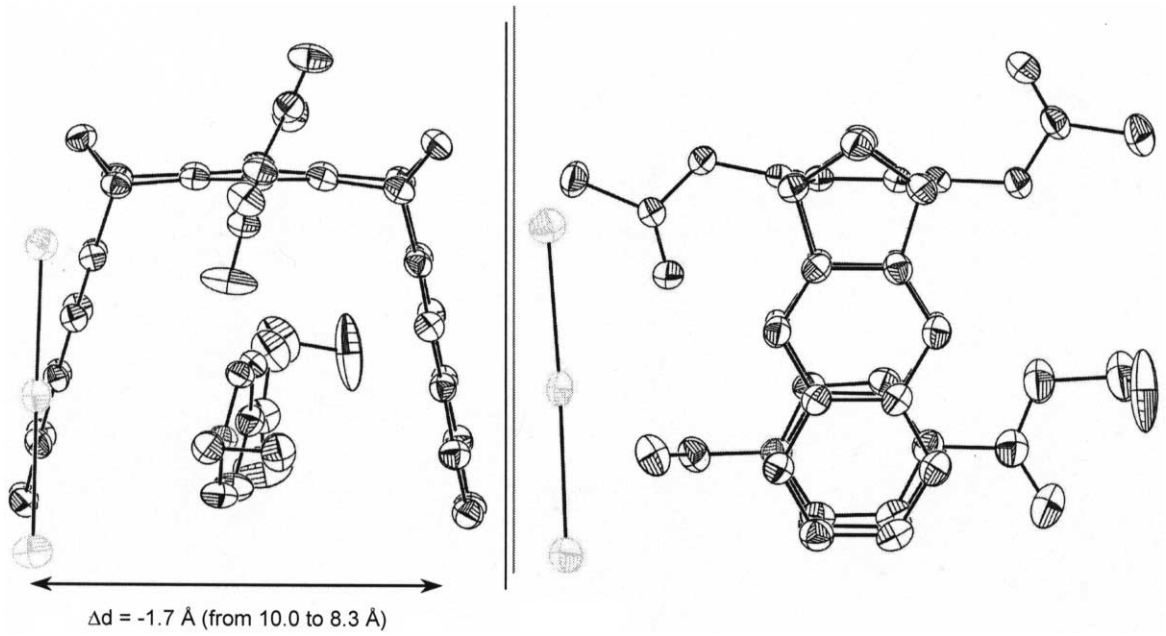


Figure 5. Single-crystal structure analysis of complex **18** @ **4b**.

Similar results are obtained for the complex between the pyridium salt **18** and diacetate clip **4b**. In solution the related *N*-ethyl-4-carbmethoxypyridinium iodide forms a relatively strong complex with **4b** as receptor (21.0°C: K_a=137 M^{-1} $CDCl_3$). The crystals suitable for the single-crystal structure analyses (Fig. 5) were obtained by cocrystallization of a (1:10) mixture of **4b** and *N*-ethyl-4-carbmethoxypyridium iodide from ethanol and dichloromethane at the air. Under these conditions, apparently, a partial air-oxidation of the iodide ions to iodine and transesterfication of the carbomethoxy group to the carbethoxy group took place leading to the salt **18** which gave the observed brownish colored cocrystals of **18** @ **4b**. The distance between the two naphthalene side walls is again reduced in the complex **18** @ **4b** from 10.0 to 8.3 Å. Remarkable is the orientation of the negatively polarized carbonyl oxygen of **4b** toward the positively charged nitrogen atom of substrate **18** (distance $(O\cdots N^+)$=3.70 Å).

Interesting cases are the complexes between tetracyanobenzene (TCNB) **19** as substrate and the dimethoxy-, diacetoxy-, and dihydroxy-substituted clips **4d**, **4b**, and **4c** as receptors. In solution no complex formation between **19** and **4d** is observed within the limits of ^1H NMR detection.[12] In the cocrystals obtained from a mixture of **19** and **4d** in chloroform a $CHCl_3$ molecule is positioned inside the cavity of **4d** whereas **19** is located between two naphthalene-units outside the cavity of **4d** (Fig. 6).

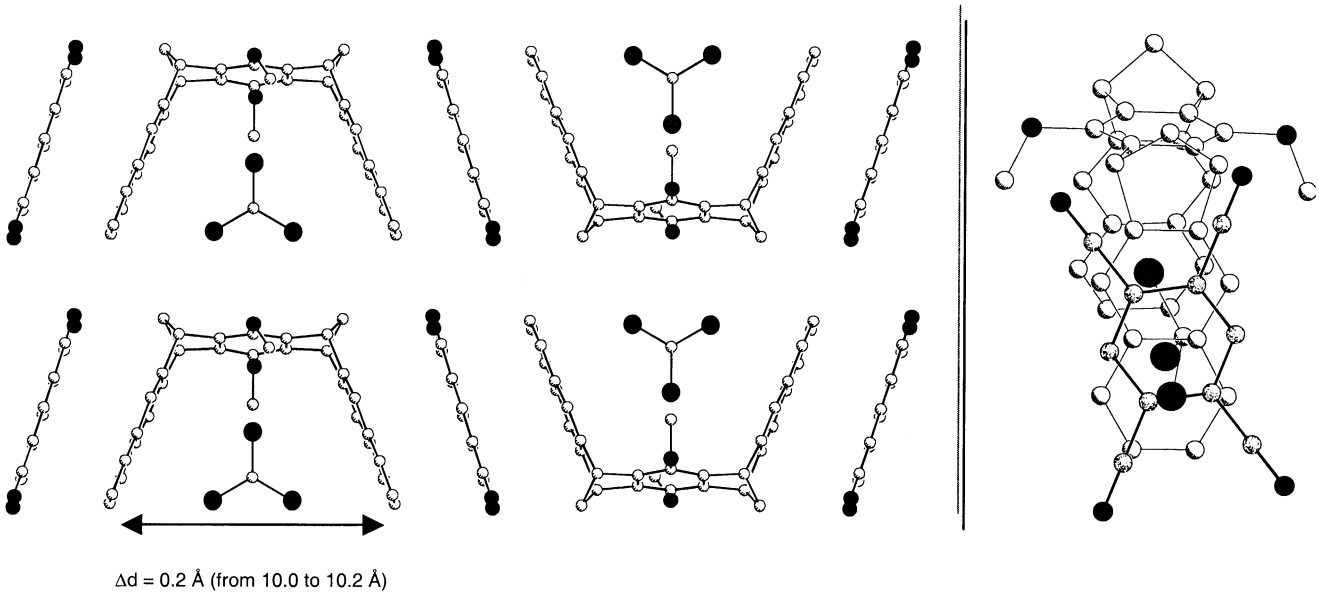


Figure 6. Single-crystal structure analysis of the cocrystals of **4d**, **19**, and $CHCl_3$ in a (1:1:1) ratio.

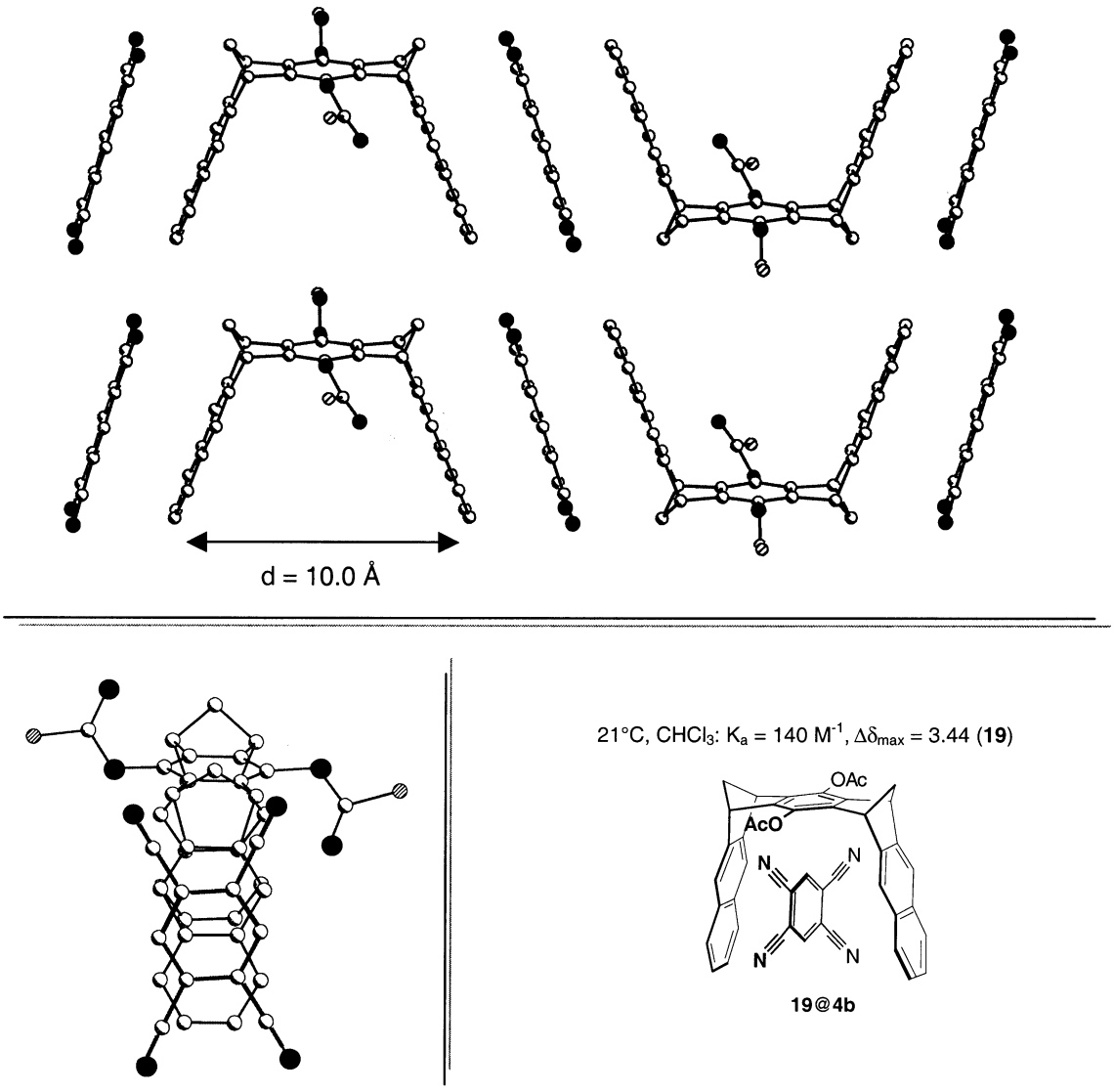


Figure 7. Comparison between the structure of the cocrystals of **4b** and **19** and the complex **19** @ **4b** in solution.

More surprising is the structure of the cocrystals between **19** and **4b** obtained from toluene and dichloromethane. In solution the diacetate clip **4b** binds TCNB **19** inside the cavity whereas in the cocrystal **19** is again located between two naphthalene-units outside the cavity of **4b** which is empty in this case (Fig. 7). Evidently, in the crystal the noncovalent interaction between **19** and the naphthalene-units of two different clip molecules is stronger than the 'intramolecular' interaction between **19** and the two naphthalene-units of one and the same clip molecule because in the first (observed) case no distortion of the clip geometry is necessary whereas in the second case a compression of the naphthalene side walls and, hence, an increase in steric strain is required for an optimal substrate–receptor interaction. Therefore the geometry of **4b** @ **19** is taken as a reference for the noncomplexed structure, which also agrees to the geometry found in semi-empirical AM1 and DFT pBP/DN* calculations. In solution, however, the (2:1) arrangement of **4b** and **19** observed in the crystal is certainly disfavored because of the highly negative entropy term expected for the formation of a trimolecular associate.

The hydroquinone clip **4c** forms a much stronger complex with TCNB **19** than the diacetate clip **4b** most likely because of the additional O–H···N hydrogen bonds (Fig. 8) and the smaller steric demand of the OH function in **4c** in comparison to that of the more bulky OAc or OMe substituent in **4b** and **4d**, respectively. In this case the substrate **19** is bound inside the cavity of **4c** in both states, in the crystalline state and as well in solution.

Encouraged by the results obtained for the complex formation between the clips **4b–d** and TCNB **19** we studied the potential receptor properties of dinaphthonorbornadiene (DNN) **20** which was synthesized by the reaction of norbornadiene with tetrabromo-*o*-xylene **6** and sodium iodide in DMF.[16] In the solution-state ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of a mixture of TCNB **19** and DNN **20** a large complexation-induced up field-shift of the TCNB protons ($\Delta\delta$) is observed. The dependence of $\Delta\delta$ from the concentration [**20**] at a constant concentration [**19**] can be best fitted by the use of the HOSTEST program[18] with the formation of (2:1) complex between **20** and **19** leading to

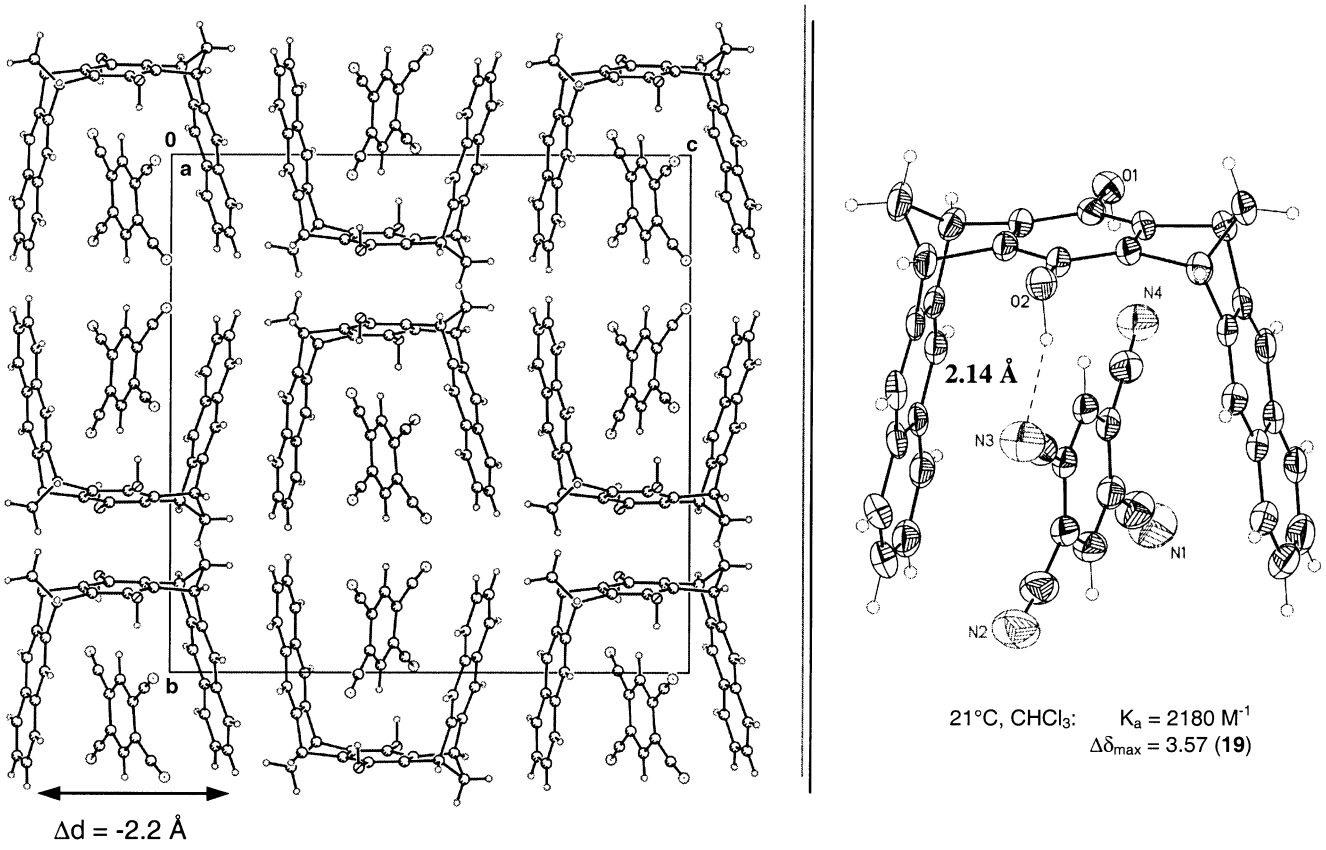
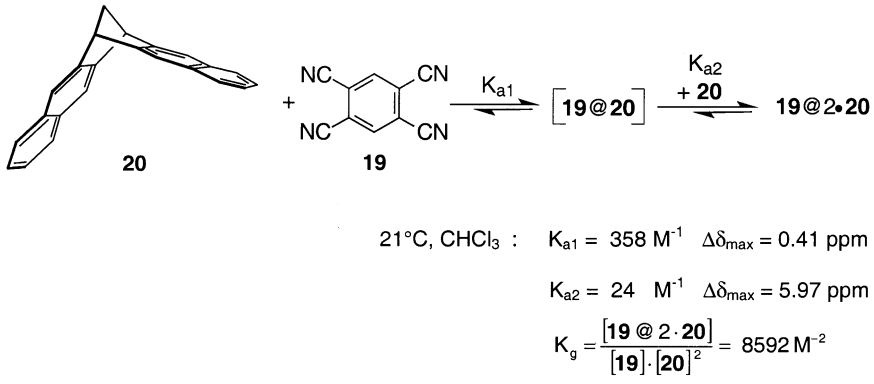


Figure 8. Single-crystal structure, association constant, and maximum complexation-induced ^{1}H NMR shift (in $CDCl_3$) of the complex **19** @ **4c**.



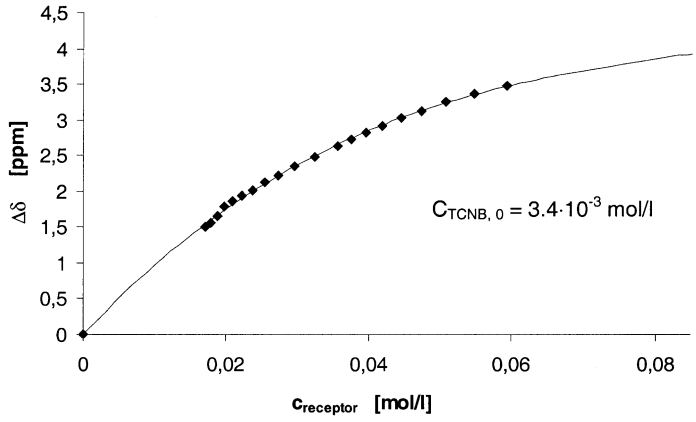


Figure 9. Dependence of the complexation-induced ^{1}H NMR shift ($\Delta\delta=\delta_{obs}-\delta_0$) of **19** (500 MHz, $CDCl_3$) from the concentration of [**20**] at a constant concentration $[\mathbf{19}]_0=3.4\times10^{-3}$ M (δ_0 (**19**)=8.25).

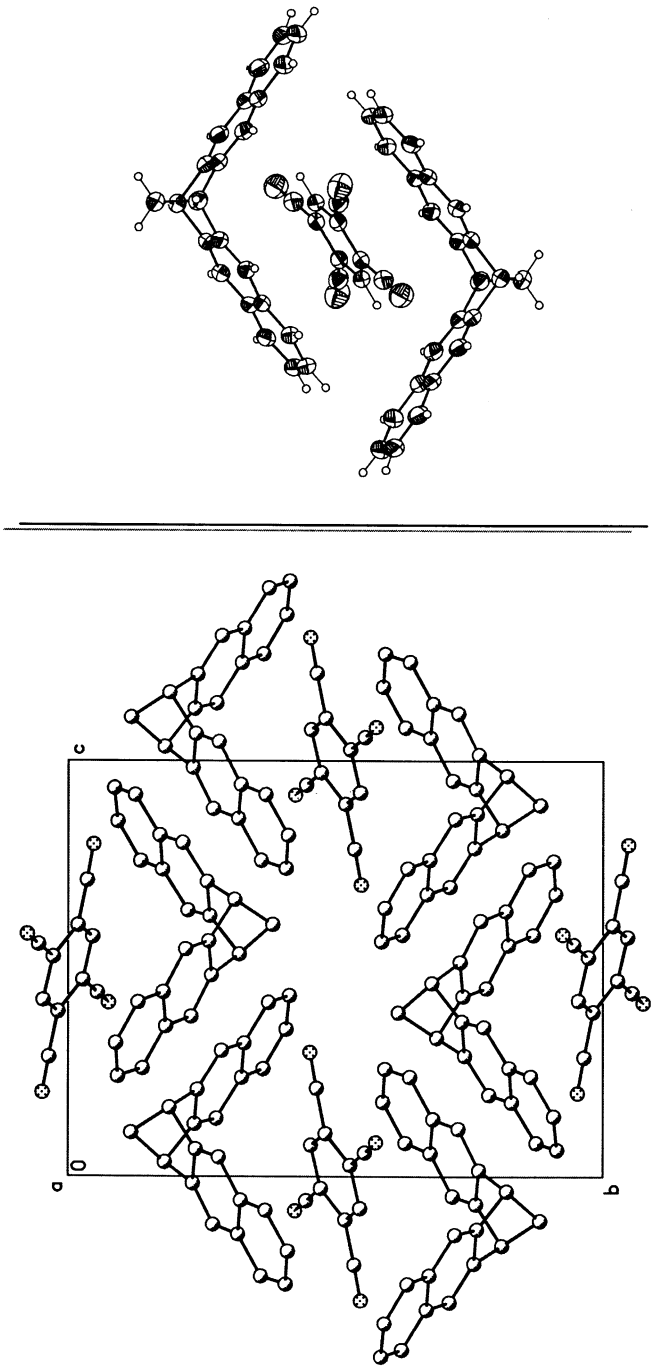


Figure 10. Single-crystal structure analysis of the complex **19** @ 2·**20**.

Table 1. Crystal data obtained from the X-ray analyses

Compound	**4b**	**13**	**13**·**2**·CH_3CN	**17** @ **4d**·**2**·EtOH	**17** @ **4d**
$T_{meas.}$ (K)	203 (2)	293 (2)	293 (2)	293 (2)	223 (1)
A (Å)	14.202 (2)	10.730 (2)[a]	9.775 (1)[a]	17.313 (3)[a]	17.401 (5)
B (Å)	25.481 (4)	8.865 (1)	15.375 (3)	21.817 (5)	18.842 (6)
C (Å)	7.368 (1)	27.421 (4)	11.355 (2)	9.209 (2)	19.806 (6)
α (°)					104.716 (7)
β (°)			110.87 (1)		92.562 (7)
γ (°)					94.682 (6)
V (Å^3)	2666.4 (7)	2608.3 (7)	1594.5 (4)	3478 (1)	6245 (3)
Z	4	4	2	4	8
ρ_{calc} (g cm^{-3})	1.302	1.331	1.259	1.357	1.350
μ (mm^{-1})	0.084	0.086	0.081	0.094	0.091
SG	*Pnma*	*Pbca*	$P2_1$/n	*Pbcn*	$P\bar{1}$
N_{total}	24434	16565	12210	22652	31022
θ_{max} (°)	24.99	24.72	26.46	24.99	25.00
N_{indep}	2394	2225	2761	2710	21995
R_{merg}	0.093	0.0416	0.0423	0.0327	0.0377
N_{obs} [4σ(F)]	1612	1671	2038	2156	13944
N_{param}	214	181	209	257	1728
R_1	0.0631	0.0552	0.0551	0.0612	0.0708
wR_2 (all data)	0.1803	0.1383	0.1544	0.1784	0.2123

[a] Ed's of cell dimensions multiplied by 10 due to a known error in diffractometer software.

up field-shift of the TCNB protons in the complex **19** @ 2·**20** of $\Delta\delta_{max}$=6.0 which is comparable to that observed for the (1:1) complex **19** @ **1a** ($\Delta\delta_{max}$=5.9).[9] The attempt, to fit the experimental data to the formation of a (1:1) complex between **19** and **20**, leads to an high $\Delta\delta_{max}$=7.0 (Fig. 9).

The results determined for the association between **19** and **20** in solution are in good agreement with single-crystal structure of the cocrystals obtained from the crystallization of a (1:1.3) mixture of **20** and **19** in toluene. In the crystalline state the complex shows an optimal arrangement of the TCNB molecule between the two DNN molecules without any distortion of the receptor geometry experiencing attractive CH–π (distance (CH···π)=2.5 Å) and slipped face-to-face π–π interactions (distance: 3.4 Å between TCNB and naphthalene, Fig. 10).

4. Conclusions

The bismethylene-bridged clips **4** reported here preferentially bind electron-deficient neutral and cationic aromatic substrates comparable to the tetramethylene-bridged tweezers **1** and **2**. The geometry of the noncovalently bound complexes with **4b**–**d** as receptors derived from the single-crystal structure analyses is, however, different from that of the complexes with **2** as receptors. In the clip complexes the substrate is placed inside the receptor cavity with its plane of molecule orientated almost parallel to the naphthalene side-walls of the receptor whereas in the tweezer complexes the substrate is orientated parallel to the central arene spacer-unit.

The findings, that TCNB **19** is positioned inside the cavity of the hydroquinone clip **4c** in solution as well as in the

Table 2. Crystal data obtained from the X-ray analyses

Compound	**18** @ **4b**	**19**, **4d**, and ·$CHCl_3$	**19**, **4b**	**19** @ **4c**	**19** @ 2·**20**
$T_{meas.}$ (K)	243 (2)	293 (2)	293 (2)	263 (2)	293 (2)
a (Å)	20.355 (9)[a]	9.672 (1)	9.685 (3)	8.203 (3)	10.378 (2)
b (Å)	19.055 (8)	30.013 (1)	29.826 (9)	19.700 (7)	15.671 (2)
c (Å)	21.922 (9)	12.939 (1)	12.603 (3)	19.702 (7)	12.668 (1)
α (°)					
β (°)					107.43 (1)
γ (°)					
V (Å^3)	8503 (6)	3755.9 (5)	3640 (2)	3184 (2)	1966 (1)
Z	8	4	4	4	4
ρ_{calc} (g cm^{-3})	2.255	1.351	1.286	1.287	1.289
μ (mm^{-1})	1.700	0.289	0.087	0.081	0.076
SG	*Pbca*	*Pnma*	*Pnma*	*Pna*2_1	$P2_1/n$
N_{total}	79736	12677	23612	5864	4739
θ_{max} (°)	23.36	24.75	25.00	25.66	27.49
N_{indep}	7485	2908	3197	5864	4499
R_{merg}	0.0376	0.0443	0.0837	0.0994	0.0350
N_{obs} [4σ(F)]	5223	2423	1781	2983	2470
N_{param}	518	258	268	433	272
R_1	0.0462	0.0690	0.0971	0.0644	0.0579
wR_2 (all data)	0.1309	0.1858	0.2745	0.1645	0.1611

[a] Ed's of cell dimensions multiplied by 10 due to a known error in diffractometer software.

crystal whereas in the case of the diacetate clip **4b** the structure of the cocrystals is different from that of the complex in solution, are particularly instructive for the understanding of the weak noncovalent binding forces. Finally, the surprising formation of a (2:1) complex between dinaphthonorbornadiene **20** and TCNB **19** in the crystal as well as in solution is a good example which shows the geometrical orientation in supramolecules affected by arene–arene interactions (Tables 1 and 2).

5. Experimental

5.1. General

IR: Bio-Rad FTS 135. UV: J+M Tidas FG Cosytec RS 422. ^{1}H NMR, ^{13}C NMR, DEPT, H,H-COSY, C,H-COSY, C,H-COSY, NOESY, HMQC, HMBC: Bruker AVANCE DRX 500; ^{1}H NMR titration experiments: Varian Gemini XL 200; the undeuterated amount of the solvent was used as an internal standard. Positions of the protons of the methano bridges are indicated by the letters i (*innen*, towards the center of the molecule) and a (*außen*, away from the center of the molecule). MS: Fisons Instruments VG ProSpec 3000 (70 eV). All melting points are uncorrected. Column chromatography: Silicagel 0.063–0.2 mm. All solvents were destilled prior to use.

5.1.1. 1,4-Dihydro-1,4-methanonaphthalene-5,8-dione (modified procedure).[14,19] To a cooled solution (10°C) of *endo*-1,2,3,4-tetrahydro-1,4-methanonaphthalene-5,8-dione (100 g, 0.57 mol) in MeOH (600 mL) was added triethylamine (1 mL) and stirred for 5 h at 10°C. The solution was allowed to warm up to room temperature and stirred for further 15 h. The solvent was removed under reduced pressure on a rotary evaporator at 40°C to give the corresponding hydroquinone, which was suspended with *p*-benzoquinone (63 g, 0.58 mol) in chloroform (1.5 L). The stirred suspension was heated first to 50°C for 4 h and then at 40°C for 1 h. The reaction mixture was cooled to room temperature, the precipitate of hydroquinone was filtered off and washed with 100 mL chloroform. The combined chloroform layers were washed with aqueous NaOH (800 mL, 1%), dried over $MgSO_4$, and concentrated in a rotary evaporator at 40°C in vacuo to give 1,4-dihydro-1,4-methanonaphthalene-5,8-dione (81 g, 81%) as an orange solid. Mp 67°C.

5.1.2. 7,16-Diacetoxy-(6α,8α,15α,17α)-6,8,15,17-tetrahydro-6,17:8,15-dimethanoheptacene 4b. The mixture of **8** (1.0 g, 3.1 mmol), tetrabromo-*o*-xylene **6** (10 g, 23.9 mmol), anhydrous NaI (23 g, 163.1 mmol), anhydrous $CaCO_3$ (5 g, 50 mmol), and anhydrous dimethyl formamide (75 mL) was stirred under Ar atmosphere for 30 min at room temperature and then heated to 55°C under vacuum (100 mbar) for 5 h. The reaction mixture was poured into ice (300 g) and the brown mixture, decolorized by the addition of aqueous sodium hydrogen sulfite, was extracted with dichloromethane (3×50 mL), the combined organic layers were filtered, washed with saturated aqueous sodium hydrogen carbonate (50 mL) and water (4×100 mL), dried over $MgSO_4$, and concentrated in vacuo in a rotary evaporator. The residue was purified by column chromatography on silica gel by using EtOAc/cyclohexane (1:3) as eluent. Digestion of the crude product after heating the suspension in methyl *tert*-butyl ether (7 mL) gave **4b** (1.35 g, 83%) as a colorless solid. Mp>300°C; MS *m/z* (%): 522 (100) [M^+], 480 (30) [M^+-CH_2CO]; HRMS *m/z* 522.182 (calcd for $C_{36}H_{26}O_4$, 522.183); IR (KBr):=3053 cm^{-1} (CH), 3011 (CH), 2984 (CH), 1766 (C=O), 1211 (C–O); ^{1}H NMR ($CDCl_3$): δ=2.35 (d, 2H, ^2J(19i-H, 19a-H)=8 Hz, 19i-H, 20i-H), 2.41 (s, 6H, $-CH_3$), 2.60 (d, 2H, 19a-H, 20a-H), 4.22 (s, 4H, 6-H, 8-H, 15-H, 17-H), 7.19 (m, 4H, 2-H, 3-H, 11-H, 12-H), 7.44 (s, 4H, 5-H, 9-H, 14-H, 18-H), 7.51 (m, 4H, 1-H, 4-H, 10-H, 13-H); ^{13}C NMR ($CDCl_3$): δ=20.91 (q, $-CH_3$), 48.04 (d, C-6, C-8, C-15, C-17), 64.9 (t, C-19, C-20), 120.08 (d, C-5, C-9, C-14, C-18), 125.24 (d, C-2, C-3, C-11, C-12), 127.65 (d, C-1, C-4, C-10, C-13), 132.12 (s, C-4a, C-9a, C-13a, C-18a), 137.18 (s, C-7, C-16), 140.72 (s, C-6a, C-7a, C-15a, C-16a), 145.78 (s, C-5a, C-8a, C-14a, C-17a), 168.71 (s, C=O).

5.1.3. 7,16-Dihydroxy-(6α,8α,15α,17α)-6,8,15,17-tetrahydro-6,17:8,15-dimethanoheptacene 4c. To a stirred suspension of **4b** (0.200 g, 0.38 mmol), phenylhydrazine (0.050 g, 0.46 mmol), and ethanol (15 mL) under argon at room temperature aqueous sodium hydroxide (0.5 mL, 15%) was added. The reaction mixture became a clear solution after about 30 min. After a reaction time of 1 h aqueous HCl (0.5 mL, 15%) was added, the reaction mixture was poured into water (50 mL), and cooled for 30 min in an ice bath. The solution was filtered under argon atmosphere, the precipitate was dried in vacuo to give **4c** (0.160 g, 95%) as a colorless solid. Mp>300°C; MS *m/z* (%): 438 (100) [M^+]; HRMS *m/z* [$M-2H]^+$ 436.143 (calcd for $C_{32}H_{20}O_2$, 436.143); IR (KBr):=3383 (OH) cm^{-1}, 3049 cm^{-1} (CH), 2991 (CH), 2968 (CH), 2932 (CH), 2860 (CH), 1503 (C=C), 1282 (C–O); ^{1}H NMR ($CDCl_3$): δ=2.45 (d, 2H, ^2J(19i-H, 19a-H)=8 Hz, 19i-H, 20i-H), 2.53 (d, 2H, 19a-H, 20a-H), 4.49 (s, 4H, 6-H, 8-H, 15-H, 17-H), 4.51 (s, 2H, OH), 7.24 (m, 4H, 2-H, 3-H, 11-H, 12-H), 7.51 (s, 4H, 5-H, 9-H, 14-H, 18-H), 7.54 (m, 4H, 1-H, 4-H, 10-H, 13-H); ^{13}C NMR ($CDCl_3$): δ=46.69 (d, C-6, C-8, C-15, C-17), 64.62 (t, C-19, C-20), 119.52 (d, C-5, C-9, C-14, C-18), 125.16 (d, C-2, C-3, C-11, C-12), 127.55 (d, C-1, C-4, C-10, C-13), 131.98 (s, C-4a, C-9a, C-13a, C-18a), 134.39 (s, C-6a, C-7a, C-15a, C-16a), 138.89 (s, C-5a, C-8a, C-14a, C-17a), 146.53 (s, C-7, C-16).

5.1.4. 7,16-Dimethoxy-(6α,8α,15α,17α)-6,8,15,17-tetrahydro-6,17:8,15-dimethanoheptacene 4d. A suspension of **4b** (0.500 g, 0.95 mmol), phenylhydrazine (0.100 g, 0.92 mmol), powdered KOH (0.300 g, 5.26 mmol) in isopropanol (20 mL) was stirred under argon for 1.5 h at room temperature. After addition of potassium *tert*-butoxide (0.100 g, 0.89 mmol) and methyl iodide (0.7 mL, 11.31 mmol) the reaction mixture was stirred for further 1.5 h at room temperature, and then poured into aqueous HCl (40 mL, 1 M). The solution was filtered, the precipitate was purified by column chromatography on silica gel by using chloroform/*n*-hexane (1:1) as eluent to give **4d** (0.406 g, 91%) as a colorless solid. Mp>210°C (sublimation); MS *m/z* (%): 466 (100) [M^+], 451 (40) [M^+-CH_3], 435 (7) [M^+-OCH_3]; HRMS *m/z* 466.198 (calcd for $C_{34}H_{26}O_2$, 466.193); IR (KBr):=3054 cm^{-1} (CH), 2990 (CH), 2951 (CH), 2920 (CH), 2826 (CH), 1504 (C=C),

1284 (C–O); ^{1}H NMR ($CDCl_3$): δ=2.35 (d, 2H, ^2J(19i-H, 19a-H)=8 Hz, 19i-H, 20i-H), 2.47 (d, 2H, 19a-H, 20a-H), 3.74 (s, 6H, $-OCH_3$), 4.47 (s, 4H, 6-H, 8-H, 15-H, 17-H), 7.18 (m, 4H, 2-H, 3-H, 11-H, 12-H), 7.44 (s, 4H, 5-H, 9-H, 14-H, 18-H), 7.51 (m, 4H, 1-H, 4-H, 10-H, 13-H). ^{13}C NMR ($CDCl_3$): δ=47.50 (d, C-6, C-8, C-15, C-17), 61.28 (q, $-OCH_3$), 64.01 (t, C-19, C-20), 119.41 (d, C-5, C-9, C-14, C-18), 125.2 (d, C-2, C-3, C-11, C-12), 127.55 (d, C-1, C-4, C-10, C-13), 132.05 (s, C-4a, C-9a, C-13a, C-18a), 139.75 (s, C-6a, C-7a, C-15a, C-16a), 145.40 (s, C-5a, C-8a, C-14a, C-17a), 147.28 (s, C-7, C-16).

5.1.5. 7,16-Bis-trifluormethylsulfonoxy-(6α,8α,15α,17α)-6,8,15,17-tetrahydro-6,17:8,15-di-methanoheptacene 4e. To an argon-swept and magnetically stirred solution of **4c** (0.100 g, 0.228), triethylamine (0.5 mL) in chloroform (10 mL) at 0°C trifluoromethanesulfonic anhydride (0.26 g, 0.92 mmol) was added dropwise. After the addition was completed, the cooling bath was removed, the mixture was warmed up to room temperature, and stirred for further 30 min. The reaction mixture was poured into ice-water (20 mL), and the layers were separated. The organic layer was washed with aqueous HCl (2×5 mL, 1 M), dried over $MgSO_4$, and concentrated in vacuo in a rotary evaporator. The residue was purified by column chromatography on silica gel by using chloroform/*n*-hexane (1:1) as eluent and finally by recrystallization from ethanol to give **4e** (0.122 g, 76%) as a colorless solid. Mp>215°C (sublimation); MS *m/z* (%): 702 (92) [M^+], 569 (16) [$M^+-CF_3SO_2$], 436 (100) [$M^+-2_*CF_3SO_2$]; HRMS *m/z* 702.062 (calcd for $C_{34}H_{20}F_6O_6S_2$, 702.061); IR (KBr):=3053 cm^{-1} (CH), 3021 (CH), 2980 (CH), 2939 (CH), 2864 (CH), 1506 (C=C); ^{1}H NMR ($CDCl_3$): δ=2.53 (d, 2H, ^2J(19i-H, 19a-H)=8 Hz, 19i-H, 20i-H), 2.71 (d, 2H, 19a-H, 20a-H), 4.62 (s, 4H, 6-H, 8-H, 15-H, 17-H), 7.27 (m, 4H, 2-H, 3-H, 11-H, 12-H), 7.58 (m, 4H, 1-H, 4-H, 10-H, 13-H), 7.60 (s, 4H, 5-H, 9-H, 14-H, 18-H); ^{13}C NMR ($CDCl_3$): δ=48.67 (d, C-6, C-8, C-15, C-17), 65.43 (t, C-19, C-20), 118.25 (q, C–F_3, ^1J(C–F)=318 Hz), 121.27 (d, C-5, C-9, C-14, C-18), 125.78 (d, C-2, C-3, C-11, C-12), 127.84 (d, C-1, C-4, C-10, C-13), 132.19 (s, C-4a, C-9a, C-13a, C-18a), 136.24 (s, C-7, C-16), 143.51 (s, C-6a, C-7a, C-15a, C-16a), 143.74 (s, C-5a, C-8a, C-14a, C-17a).

5.1.6. (6α,8α,15α,17α)-6,8,15,17-Tetrahydro-6,17:8,15-dimethanoheptacene 4a. A suspension of **4e** (0.294 g, 0.42 mmol), 1,3-bis(diphenylphosphino)propane (0.066 g, 0.16 mmol), bis(triphenylphosphino)palladium(II)chloride (0.039 g, 0.06 mmol), and formic acid (0.4 mL) in dimethyl formamide (5 mL) and tri-*n*-butylamine (1 mL) was stirred under argon at 100°C for 72 h. After addition of aqueous HCl (30 mL, 1.5 M), the mixture was extracted with methyl *tert*-butyl ether (3×7 mL), the combined organic layers were washed with aqueous HCl (3×5 mL, 1.5 M), and dried over $MgSO_4$. The organic layer was concentrated in vacuo in a rotary evaporator. Purification of the yellow residue by column chromatography (silica gel, chloroform/*n*-hexane 1:1) yielded **4a** as colorless crystals (0.145 g, 85%). Mp>200°C (sublimation); IR (KBr):=3065 cm^{-1} (CH), 2992 (CH), 2951 (CH), 2924 (CH), 2838 (CH), 1500 (C=C); ^{1}H NMR ($CDCl_3$): δ=2.50 (d, 2H, ^2J(19i-H, 19a-H)=8 Hz, 19i-H, 20i-H), 2.58 (d, 2H, 19a-H, 20a-H), 4.28 (s, 4H, 6-H, 8-H, 15-H, 17-H), 7.23 (m, 4H, 2-H, 3-H, 11-H, 12-H), 7.27 (s, 2H, 7-H, 16-H), 7.49 (s, 4H, 5-H, 9-H, 14-H, 18-H), 7.55 (m, 4H, 1-H, 4-H, 10-H, 13-H); ^{13}C NMR ($CDCl_3$): δ=50.62 (d, C-6, C-8, C-15, C-17), 65.27 (t, C-19, C-20), 116.25 (s, C-7, C-16), 119.22 (d, C-5, C-9, C-14, C-18), 125.01 (d, C-2, C-3, C-11, C-12), 127.49 (d, C-1, C-4, C-10, C-13), 132.03 (s, C-4a, C-9a, C-13a, C-18a), 147.05 (s, C-6a, C-7a, C-15a, C-16a), 147.53 (s, C-5a, C-8a, C-14a, C-17a).

5.1.7. 7,18-Diacetoxy-(6α,9α,16α,19α)-6,9,16,19-tetrahydro-6,19:9,16-dimethanooctacene 5b. The mixture of **10** (1.16 g, 3.1 mmol), tetrabromo-*o*-xylene **6** (10 g, 23.9 mmol), anhydrous NaI (23 g, 163.1 mmol), anhydrous $CaCO_3$ (5 g, 50 mmol), and anhydrous dimethyl formamide (75 mL) was stirred under Ar atmosphere for 30 min at room temperature and then heated to 55°C under vacuum (100 mbar) for 5 h. The reaction mixture was poured into ice (300 g) and the brown mixture, decolorized by the addition of aqueous sodium hydrogen sulfite, was extracted with dichloromethane (3×50 mL), the combined organic layers were filtered, washed with saturated aqueous sodium hydrogen carbonate (50 mL) and water (4×100 mL), dried over $MgSO_4$, and concentrated in vacuo in a rotary evaporator. Purification of the yellow oil by column chromatography (silica gel, EtOAc/cyclohexane 1:3) yielded **5b** as colorless crystals as a colorless solid (1.40 g, 79%). Mp 197–202°C; MS *m/z* (%): 572 (35) [M^+], 530 (30) [M^+-CH_2CO], 488 (100) [$M^+-2_*CH_2CO$]; HRMS *m/z* 572.191 (calcd for $C_{40}H_{28}O_4$, 572.199); IR (KBr):=3050 cm^{-1} (CH), 3013 (CH), 2984 (CH), 1760 (C=O), 1219 (C–O); ^{1}H NMR ($CDCl_3$): δ=2.47 (d, H, ^2J(21i-H, 21a-H)=8 Hz, 21a-H), 2.54 (s, 2H, 22i-H, 22a-H), 2.55 (s, 6H, $-CH_3$), 2.60 (d, H, ^2J(21i-H, 21a-H)=8 Hz, 21i-H), 4.44 (s, 2H, 6-H, 19-H), 4.47 (s, 2H, 9-H, 16-H), 7.27 (m, 4H, 2-H, 3-H, 12-H, 13-H), 7.56 (s, 2H, 10-H, 15-H), 7.57 (m, 2H, 11-H, 14-H), 7.58 (s, 2H, 8-H, 17-H), 7.60 (s, 2H, 5-H, 20-H), 7.62 (m, 2H, 1-H, 4-H); ^{13}C NMR ($CDCl_3$): δ=20.90 (q, $-CH_3$), 47.97 (d, C-6, C-19), 50.47 (d, C-9, C-16), 62.0 (t, C-21), 62.68 (t, C-22), 113.44 (d, C-8, C-17), 119.68 (d, C-10, C-15), 120.37 (d, C-5, C-20), 125.21 (d, C-2, C-3), 125.24 (d, C-12, C-13), 125.50 (s, C-7a, C-17a), 127.55 (d, C-11, C-14), 127.69 (d, C-1, C-4), 132.21 (s, C-10a, C-14a), 132.29 (s, C-4a, C-20a), 137.09 (s, C-7, C-18), 137.39 (s, C-6a, C-18a), 144.78 (s, C-5a, C-19a), 146.06 (s, C-8a, C-16a), 147.68 (s, C-9a, C-15a), 168.92 (s, C=O).

5.1.8. 7,16-Diacetoxy-(6α,8β,15β,17α)-6,8,15,17-tetrahydro-6,17:8,15-dimethanoheptacen 13. The mixture of **12** (1.0 g, 3.1 mmol), tetrabromo-*o*-xylene **6** (10 g, 23.9 mmol), anhydrous NaI (23 g, 163.1 mmol), anhydrous $CaCO_3$ (5 g, 50 mmol), and anhydrous dimethyl formamide (75 mL) was stirred under Ar atmosphere for 30 min at room temperature and then heated to 55°C under vacuum (100 mbar) for 5 h. The reaction mixture was poured into ice (300 g) and the brown mixture, decolorized by the addition of aqueous sodium hydrogen sulfite, was extracted with dichloromethane (3×50 mL), the combined organic layers were filtered, washed with saturated aqueous sodium hydrogen carbonate (50 mL) and water (4×100 mL), dried over $MgSO_4$, and concentrated in vacuo in a rotary evaporator. The residue was purified by column chromatography on silica gel by using EtOAc/cyclohexane (1:3) as eluent. Recrystallization of the crude product from toluene gave

13 (0.89 g, 55%) as a colorless solid. Mp>300°C; MS *m/z* (%): 522 (77) [M^+], 480 (38) [M^+-CH_2CO], 438 (100) [$M^+-2_*CH_2CO$], 43 (10) [CH_3CO^+]; HRMS *m/z* 522.182 (calcd for $C_{36}H_{26}O_4$, 522.183); IR (KBr):=3063 cm^{-1} (CH), 3015 (CH), 2991 (CH), 1754 (C=O), 1208 (C–O); ^1H NMR ($CDCl_3$): δ=2.35 (d, 2H, ^2J(19i-H, 19a-H)=8 Hz, 19i-H, 20i-H), 2.47 (d, 2H, 19a-H, 20a-H), 2.49 (s, 6H, $-CH_3$), 4.26 (s, 4H, 6-H, 8-H, 15-H, 17-H), 7.34 (m, 4H, 2-H, 3-H, 11-H, 12-H), 7.61 (s, 4H, 5-H, 9-H, 14-H, 18-H), 7.69 (m, 4H, 1-H, 4-H, 10-H, 13-H); ^{13}C NMR ($CDCl_3$): δ=20.84 (q, $-CH_3$), 48.08 (d, C-6, C-8, C-15, C-17), 64.20 (t, C-19, C-20), 120.18 (d, C-5, C-9, C-14, C-18), 125.30 (d, C-2, C-3, C-11, C-12), 127.8 (d, C-1, C-4, C-10, C-13), 132.22 (s, C-4a, C-9a, C-13a, C-18a), 137.45 (s, C-7, C-16), 140.66 (s, C-6a, C-7a, C-15a, C-16a), 145.99 (s, C-5a, C-8a, C-14a, C-17a), 168.41 (s, C=O).

5.2. Preparation of crystals suitable for single-crystal structure analysis

5.2.1. 4b. To a suspension of **4b** (0.025 g, 0.048 mmol), pyrazine (0.1 g, 1.25 mmol) and ethanol (3 mL) at 35°C was added so much dichloromethane that it became a clear colorless solution. Crystallization of **4b** occurred during slow evaporation of the solvents. After one week, colorless plates **4b** suitable for single-crystal structure analysis were obtained.

5.2.2. 13. The crystallization of **13** from acetonitrile occurring during slow evaporation of the solvent leads to two different type of crystals, plates containing only **13** and needles containing **13** and acetonitril in a (1: 2) ratio.

5.2.3. 17 @ 4d. To a suspension of **4d** (0.025 g, 0.048 mmol) and **17** (0.01 g, 0.06 mmol) in ethanol (2 mL) at 35°C so much dichloromethane was added that it became a clear orange solution. Crystallization occurred during slow evaporation of the solvents. After one week, cocrystals containing complex **17** @ **4d** and EtOH in a (1:2) ratio suitable for single-crystal structure analysis were obtained as orange needles. The cocrystals containing ethanol were kept in a sealed flask at room temperature for about 1.5 years. During this time **17** @ **4d** precipitates as orange plates which do not contain ethanol.

5.2.4. 19 and 4b. To a suspension of **4b** (0.025 g, 0.048 mmol) and **19** (0.012 g, 0.07 mmol) in toluene (3 mL) at 40°C so much dichloromethane was added that it became a clear yellow solution. The solvents were slowly evaporated by leaving the flask open. After 3 d, yellow plates of complex **19** @ **4b** suitable for single-crystal structure analysis were obtained.

5.2.5. 19, 4d, and $CHCl_3$. Crystallization occurred during slow evaporation of the solvent of a chloroform solution containing **4d** (0.04 g, 0.085 mmol) and **19** (0.016 g, 0.089 mmol). After one week, yellow bricks containing complex **19**, **4d**, and $CHCl_3$ in a (1:1:1) ratio suitable for single-crystal structure analysis were obtained.

5.2.6. 19 @ 4c. To a suspension of **4c** (0.025 g, 0.057 mmol) and **19** (0.012 g, 0.07 mmol) in toluene (7 mL) at 70°C under argon so much chloroform was added that it became a clear yellow solution. The solution was cooled down to 40°C. After 12 h under a slight argon stream, yellow needles of complex **19** @ **4c** suitable for single-crystal structure analysis were obtained.

5.2.7. 19 @ 2·20. To a suspension of **20** (0.016 g, 0.054 mmol) and **19** (0.012 g, 0.07 mmol) in toluene (3 mL) at 40°C so much dichloromethane was added that it became a clear yellow solution. The crystallization occurred during slow evaporation of the solvent. After three days, yellow plates of complex **19** @ 2·**20** suitable for single-crystal structure analysis were obtained.

5.2.8. 18 @ 4b. To a suspension of **4b** (0.025 g, 0.047 mmol) and *N*-ethyl-4-carbmethoxypyridinium iodide (0.1 g, 0.34 mmol) in ethanol (3 mL) at 35°C so much dichloromethane was added that it became a clear yellow solution. The crystallization occurred during slow evaporation of the solvent. After 14 days, brown bricks of complex **18** @ **4b** suitable for single-crystal structure analysis were obtained.

5.3. Determination of K_a by ^1H NMR titration

In the titration experiments, the total substrate concentration $[S]_0$ was kept constant whereas the total receptor concentration $[R]_0$ was varied. This was achieved by dissolving a defined amount of the receptor R in 0.5 mL of a solvent containing the substrate concentration $[S]_0$. $\Delta\delta$ was determined from the chemical shift of the pure substrate and the chemical shift of the substrate measured in the ^1H NMR spectrum (200 MHz, 21°C) of this mixture. Successive addition of further solution containing $[S]_0$ led to a dilution of the concentration $[R]_0$ in the mixture while $[S]_0$ was kept constant. Measurement of the chemical shift of the substrate dependent from the concentration $[R]_0$ afforded the data pairs $\Delta\delta$ and $[R]_0$. Fitting of the data to the (1:1) binding isotherm by iterative methods delivered the parameters K_a and $\Delta\delta_{max}$.[20,21]

5.4. Crystal structure determinations

X-Ray data were collected on a Brucker-SMART 1000 System, except for **19** @ 2·**20**, which was measured on a Siemens P4 diffractometer. Structure solutions and refinements were performed with the Siemens SHEXTL-suite of programs (Version 5.10), hydrogen atoms were treated as riding groups with the 1.2-fold of the corresponding C-atom.

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