Synthesis and Supramolecular Properties of Trimethylene-Bridged Clips

Frank-Gerrit Klärner,*[a] Matthias Lobert,[a] Ulf Naatz,[a] Heinz Bandmann,[a] and Roland Boese[b]

Dedicated to Professor Lutz F. Tietze on the occasion of his 60th birthday

Abstract: The novel trimethylene-bridged clips **3** and **4** have been synthesized by using repetitive stereoselective Diels–Alder reactions of the benzo- and naphthobismethylenenorbornenes **8** and **19** as dienes and norbornadiene **9** as bisdienophile, and subsequent dehydrogenation of the primary cyclobisadducts **10** and **20** by using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). Clips **3** and **4** serve as receptors for a variety of electron-deficient neutral and cationic aromatic substrates, comparable to the molecular tweezers **1** and **2**. The thermodynamic parameters of the complex formation, K_a and ΔG, were determined by ^{1}H NMR titration experiments and, in the case of the highly stable complex TCNB **32@4**, by the use of isothermal titration microcalorimetry. The finding that clip **4** forms more stable complexes than **3** can be explained by the larger van der Waals contact surfaces of the naphthalene sidewalls in **4** compared to the corresponding benzene systems in **3**. In the complexes with **4** as receptor, the plane of each aromatic substrate molecule is calculated to be oriented almost parallel to the naphthalene sidewalls. However, in the complexes of tweezers **2**, the substrate is usually oriented parallel to the central naphthalene spacer unit. Due to the more open topology of **4**, most complexes were calculated to consist of two or more equilibrating noncovalent conformers.

Keywords: arene–arene interaction · Diels–Alder reactions · host–guest systems · molecular clips and tweezers · molecular recognition

Introduction

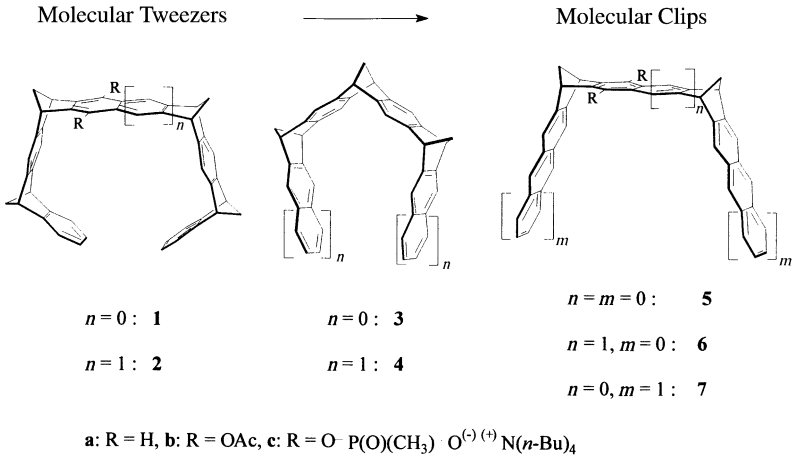
The processes of molecular recognition and self-assembly are of central importance in many areas of biological and supramolecular chemistry, for example in protein folding, enzyme–substrate binding, antigen–antibody recognition, and in the design of new materials by molecular self-assembly.[1, 2] All these processes depend on specific, mostly noncovalent receptor–substrate interactions. Besides the relatively strong and therefore often dominating hydrogen bonding,[3] ion pairing,[4, 5] and the hydrophobic effect in aqueous media,[6] the noncovalent interactions of arenes with other aromatic units ($\pi-\pi$ and CH$-\pi$ interactions)[7] or with positively charged ions (cation-π interaction)[5, 8] seem to be particularly important for the formation of supramolecules. The design of efficient synthetic receptors with the ability to selectively bind substrates requires precise control of their topological and electronic properties. Besides cyclic and hence well-preorganized receptors (e.g. cyclodextrins,[9] cyclophanes,[10] carcerands,[11] and cryptophanes[12]) and the more recently reported supramolecular capsules[13] formed by self-assembly of suitable building blocks, noncyclic receptors with cavities of flexible size proved to be effective.[1, 14] Recently, we have described the synthesis of the benzene- and naphthalene-spaced receptors **1** and **2**.[15–17] These belong to a family of molecules termed molecular tweezers[18] due to their concave–convex topology and their propensity to selectively form complexes with electron-deficient aliphatic and aromatic substrates as well as with organic cations. This is achieved by clipping the substrate between the tweezers' tips, comparable to the working principle of mechanical tweezers. Tweezers **1** or **2**, however, do not bind electron-rich arenes or anions. This high selectivity has been correlated with markedly negative molecular electrostatic potentials calculated for the concave sides of **1** and **2** by using quantum-chemical methods.[19, 20] When analogous calculations were performed for the electron-deficient substrates, the complementary nature of their electrostatic potentials to the electrostatic potentials found for the inside of the cavity of **1** or **2** became evident. This suggests that the relatively strong receptor–substrate binding is predominantly of electrostatic nature.

[a] Prof. Dr. F.-G. Klärner, Dipl.-Chem. M. Lobert, Dr. U. Naatz, Dipl.-Ing. H. Bandmann
Institut für Organische Chemie der Universität Duisburg-Essen
45117 Essen (Germany)
Fax: (+49) 201-1834252
E-mail: frank.klaerner@uni-essen.de

[b] Prof. Dr. R. Boese
Institut für Anorganische Chemie der Universität Duisburg-Essen
45117 Essen (Germany)

Supporting information for this article is available on the WWW under http://www.chemeurj.org or from the author.

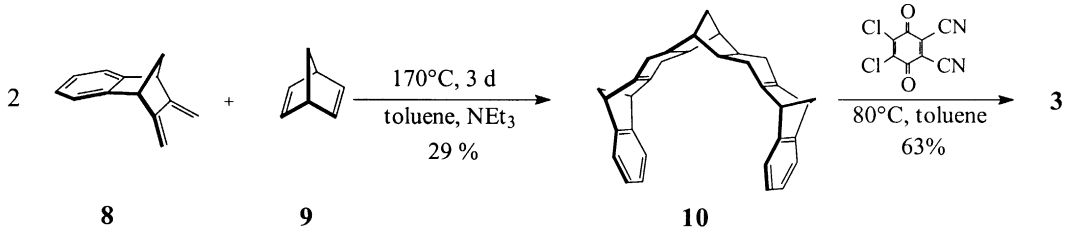
DOI: 10.1002/chem.200304919



To investigate the effect of the receptor topology on the substrate specificity, the number of methylene bridges was reduced from four in the molecular tweezers **1** and **2** to two in **5**,[21, 22] **6**,[21, 23] and **7**.[24] We call the dimethylene-bridged systems **5**, **6**, and **7** *molecular clips* because **5** and **7** form complexes by placing the aromatic substrate inside the receptor cavity. The molecular plane of such a substrate molecule is almost parallel to the naphthalene or anthracene sidewalls of the receptor. This is in contrast to the geometry of the hitherto known complexes of the tweezers **2** as receptor, where the plane of the substrate molecule is arranged nearly parallel to the central naphthalene spacer-unit of **2**.[15–17] Due to their more open cavities, the clips are expected to be less specific to the size and shape of the substrate than the tweezers. According to single-crystal structure analyses, the distance between the naphthalene sidewalls in **5** have to be compressed from about 10 Å in the empty receptor to approximately 8 Å in the complex to gain attractive noncovalent substrate–receptor interactions.[21] The increase in steric strain resulting from this compression certainly explains why the complexes of **5** are weaker than those of **2**. However, most-recent results obtained with the water-soluble diphosphonate-substituted clip **5c** showed that it forms highly stable complexes with *N*-alkylpyridinium salts such as *N*-methylnicotinamide iodide or NAD^+ (association constant $K_a = 83100$ and $9100\,M^{-1}$, respectively) in aqueous solution.[22] Here we report the synthesis and the supramolecular properties of the trimethylene-bridged clips **3** and **4**, the missing links between the di- and tetramethylene-bridged systems.

Results

Synthesis of the trimethylene-bridged clips 3 and 4: The two-step synthesis of **3** by a repetitive Diels–Alder reaction of diene **8** with norbornadiene **9** as bisdienophile and subsequent dehydrogenation by using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) has already been published in a short communication (Scheme 1).[25] The bowl-shaped structure of **3** was unambiguously determined by single-crystal structure analysis (Figure 1) and the spectral data (see Experimental



Scheme 1. Two-step synthesis of clip **3.**

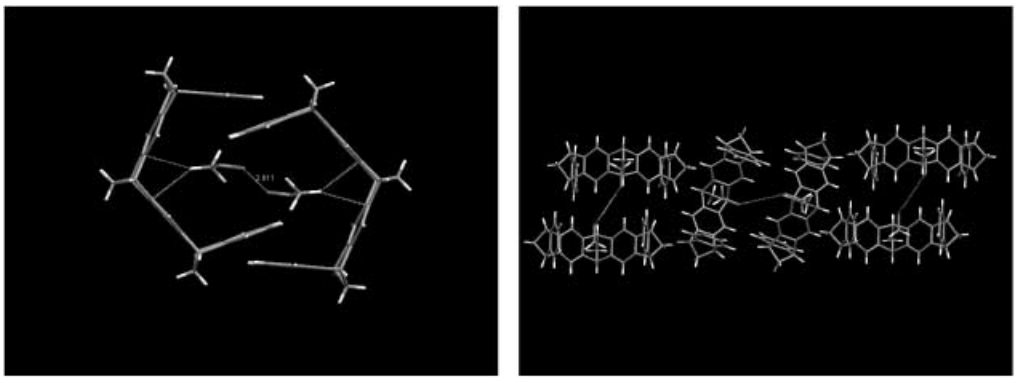


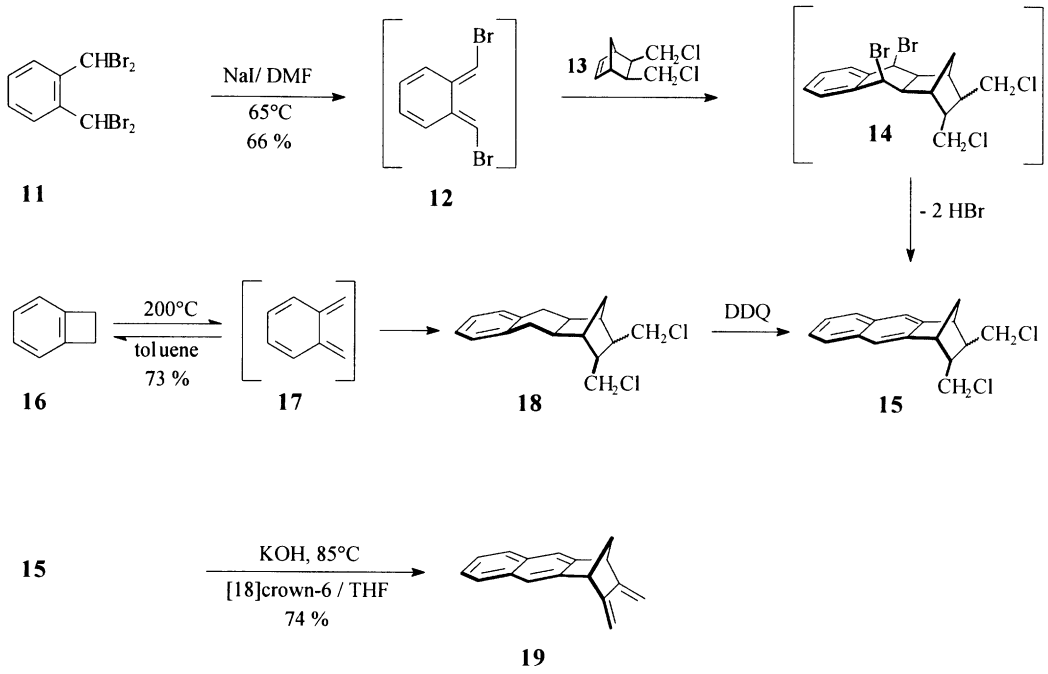
Figure 1. Single-crystal structure analysis of the complex of **3** with ethanol; left: the centrosymmetric dimer with the O–H···O bridge at $d = 2.811$ Å, right: the crystal lattice

Section). Crystal structures could be determined for the complexes of **3** with either ethanol only or with ethanol and water. Heavy disorder does not allow for interpretation and discussion of the details for the latter analysis. The complex with ethanol, however, provided a crystal structure of a centrosymmetric dimer with O–H ··· O bridges at $d = 2.811$ Å in which only the oxygen atoms are disordered (Figure 1 left). These dimers link the host molecules which are shifted to form double brick steps, as shown in Figure 1 right.

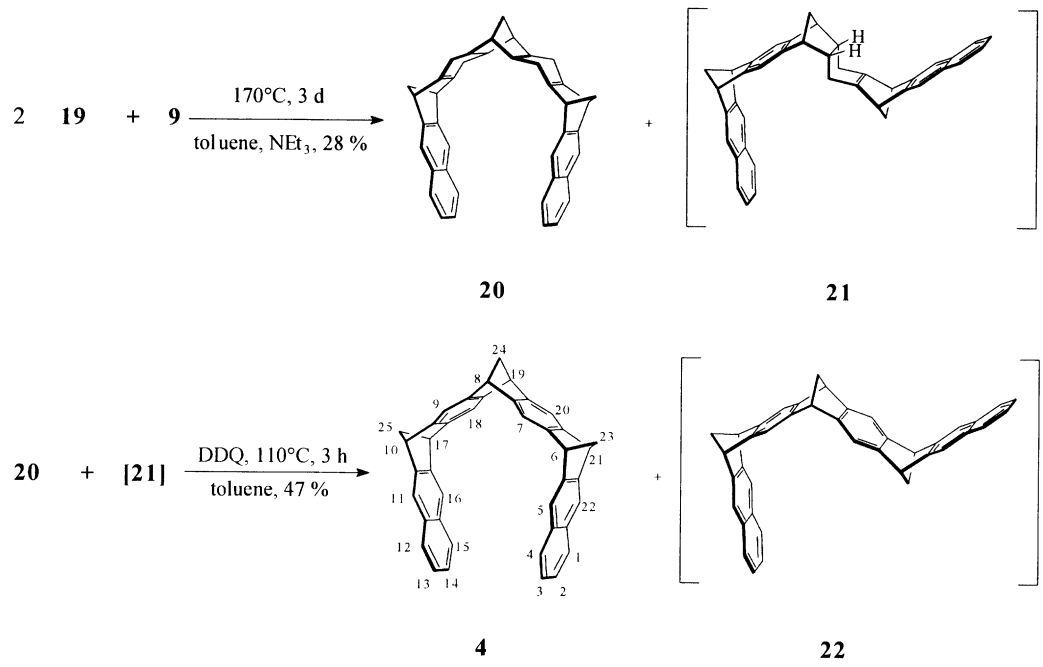
The high stereoselectivity of the Diels–Alder reaction between **8** and **9** was surprising, because norbornadiene **9** does not generally show complete *exo* selectivity and, for example, gives a (60:40) mixture of the *syn* and *anti* adduct in the Diels–Alder reaction with 5,6-bismethylenenorbornene as diene.[26]

Encouraged by these results, we tried to synthesize the dinaphtho-substituted trimethylene-bridged clip **4** by an analogous route. The hitherto unknown diene **19** could be prepared in two different ways. The first synthesis of **19** starts with the in situ generation of dibromo-*o*-quinodimethane **12** by 1,4-Br_2 elimination from tetrabromo-*o*-xylene **11** with sodium iodide as nucleophile (Scheme 2). This reaction has been already described by Cava et al. in 1960.[27] In the absence of a trapping reagent, the highly reactive *o*-quinodimethane derivative **12** undergoes an electrocyclic ring closure yielding 3,4-dibromo-1,2-benzocyclobutene, which can also be used as a precursor in the preparation of **12** at higher temperature (150 °C). In the presence of a dienophile such as maleic anhydride or *N*-phenyl maleic imide, **12** reacts with these trapping reagents leading to the corresponding naphthalene derivatives after double HBr elimination of the primary Diels–Alder adducts under the given reaction conditions. Later, in 1986, Paddon-Row and Patney[28] used this method to annulate naphthalene units to norbornene and norbornadiene systems. The reaction of **11** with sodium iodide at 65 °C, in the presence of norbornene **13**,[29] leads to the corresponding naphtho-substituted norbornene **15** in 66% yield. Product **15** is also available from a second route starting from benzocyclobutene **16**.[30] **16** undergoes an electrocyclic ring-opening at 200 °C, yielding *o*-quinodimethane **17**[31] which can be trapped by norbornene **13** to produce the Diels–Alder adduct **18**. It is not necessary to isolate **18**, which can immediately be dehydrogenated by DDQ to give the naphtho-substituted norbornene **15**. Although the overall yield of the second route (73%) is slightly higher than that of the first one (66%), we preferred to prepare **15** by the first route owing to the better availability of **11** compared to **16**. Twofold HCl elimination of **15** with potassium hydroxide in the presence of crown ether ([18]crown-6) in THF leads to the desired diene **19** in 74% yield.

Repetitive Diels–Alder reactions between the diene **19** and the bisdienophile **9** in toluene at 170 °C produced an 11:1 mixture of the *all-syn*- and *syn-anti*-bisadducts **20** and **21** (Scheme 3). The *syn*-bisadduct **20** precipitates after cooling the reaction mixture to room temperature, and after this to −15 °C in the refrigerator for one night (yield of isolated **20**: 28%).[32] Compound **20** is converted into the desired trimethylene-bridged clip **4** by oxidative DDQ dehydrogenation in 47% yield. The symmetric structure of **4** can be unambiguously assigned from its ^{1}H NMR spectrum, displaying a singlet at $\delta = 2.4$ ppm and an AB spectrum at $\delta = 2.3$, 2.5 ppm for the CH_2 protons of the central (C-24) and the peripheral methylene bridges (C-23, C-25) respectively. The 1:2 splitting of the bridgehead protons into two signals at $\delta = 4.00$ and 4.17 ppm, assigned to the central and peripheral norbornadiene-units (8, 19-H_2 and 6, 21, 10, 17-H_4), respectively, and that of the aromatic protons (singlets at $\delta = 7.13$ (7, 20, 9, 18-H_4) and 7.40 ppm (5, 22, 11, 16-H_4)) and the AA′BB′ spectrum at $\delta = 7.15$, 7.44 ppm (1, 2, 3, 4, 12, 13, 14, 15-H_8) assigned to the isolated and terminal protons of the benzene- and



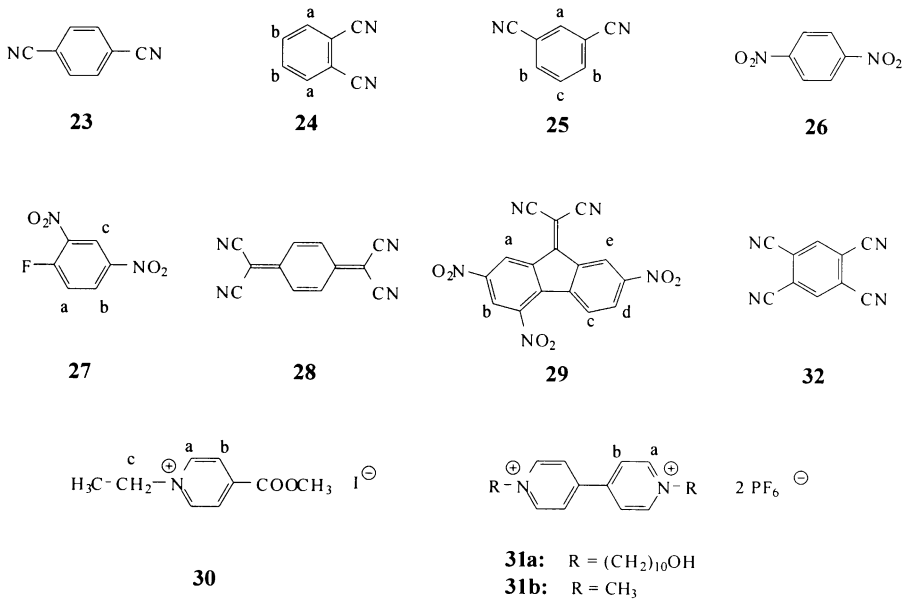
Scheme 2. Two possible routes for the production of compound **15**, which, upon further reaction, yield diene **19**.



Scheme 3. Synthesis of the trimethylene-bridged clip **4.**

naphthalene units, respectively, are well in accord with the symmetrical structure **4**.

The trimethylene-bridged blips 3 and 4 as receptors for electron-deficient substrates: Due to their ribbon-type concave topology, the four arene units of the trimethylene-bridged clips **3** and **4** define a cavity in which a substrate can be bound by multiple noncovalent arene–arene interactions. This is comparable to the molecular tweezers **1** and **2** in which the cavity is shaped by five arene units. The magnetic anisotropy of the arene units makes ^{1}H NMR spectroscopy a very sensitive method for the detection of substrates bound inside the cavity of **3** and **4**.[33] In the ^{1}H NMR spectrum of a mixture of clip **4** and *p*-dicyanobenzene **23** in $CDCl_3$ ($[\mathbf{4}]_0 =$ 0.0167 M, $[\mathbf{23}]_0 = 0.0067$ M), the formation of the complex **23@4** can easily be detected by the upfield shift of the signal of **23** induced by the presence of **4** ($\Delta\delta_{obs} = \delta_0 - \delta_{obs} = 1.1$, δ_0 is the chemical shift of the protons of **23** in the absence of **4**). The association constant $K_a = [\mathbf{23@4}]/[\mathbf{23}]\cdot[\mathbf{4}] = 43 \pm 4\ \text{M}^{-1}$ and the maximum complexation-induced shift $\Delta\delta_{max} = 2.8$ ppm in the complex **23@4** were determined at 24 °C from the dependence of $\Delta\delta_{obs}$ on the concentration of **4** at a constant concentration $[\mathbf{23}]_0$ by the use of an iterative nonlinear regression analysis (Figure 2).[34] The clips **3** and **4** are able to form host–guest complexes with a variety of electron-deficient substrates (Table 1). The maximum complexation-induced shifts $\Delta\delta_{max}$, the association constants K_a, and, hence, the Gibbs enthalpies ΔG of association were determined by the use of ^{1}H NMR titration experiments as described for the formation of **23@4**.



Job-plot analyses were performed to determine the stoichiometry of the complexes **4@28** and **4@30** as representative examples. In both cases the plot of the mole fraction χ ($\chi = [S]_0/([R]_0 + [S]_0)$, S: substrate, R: receptor) versus the mole fraction multiplied by the complexation-induced ^{1}H NMR shift of the substrate, $\chi\Delta\delta_{obs}$, shows a maximum at $\chi = 0.5$. This provides good evidence of a 1:1 stoichiometry for the complexes **4@28**, and **4@30**, respectively (for example, the Job plot of **30** is shown in Figure 3).[35] Additionally the evaluation of the ^{1}H NMR titration data by

Table 1. The comparison of $\Delta\delta_{max}$, K_a [M^{-1}], and ΔG [kcal mol^{-1}] for the formation of complexes between the clips **3** and **4** and the tweezer **2a**, respectively, as receptors and substrates **23–32** in $CDCl_3$ at 24 °C (titration experiments of **2a** and **4** as receptors) and 25 °C (titration experiments of **3** as receptor)

Substrate	Receptor								
	4			**3**[c]			**2a**		
	$\Delta\delta_{max}$	K_a	ΔG	$\Delta\delta_{max}$	K_a	ΔG	$\Delta\delta_{max}$	K_a	ΔG
23	2.9	43	−2.2	0.61	10	−1.4	4.3	110	−2.8
24	3.4 (H^a)	10	−1.4		–		4.4 (H^a)	40	−2.1
	3.4 (H^b)						2.6 (H^b)		
25	1.5 (H^a)	39	−2.2		–		5.4 (H^a)	85	−2.6
	1.7 (H^b)						4.6 (H^b)		
	1.2 (H^c)						2.6 (H^c)		
26	3.2	56	−2.4	–	< 10	–	5.5	45	−2.2
27	4.3 (H^a)	48	−2.3	3.0 (H^a)	13	−1.5		< 1 [a]	
	3.8 (H^b)			2.9 (H^b)					
	3.3 (H^c)			0.9 (H^c)					
28	3.3	2600	−4.6	1.9	25	−1.9	3.6	> 10^5 [b]	–
29[c]	1.1 (H^a)	130	−2.9	0.2 (H^a)	10	−1.4		–[d]	
	1.5 (H^b)			0.7 (H^b)					
	4.6 (H^c)			2.9 (H^c)					
	4.0 (H^d)			3.1 (H^d)					
	2.1 (H^e)			0.9 (H^e)					
30[c]	3.5 (H^a)	410	−3.6	2.4 (H^a)	29	−2.0	4.2 (H^a)	1100	−4.1
	3.4 (H^b)			1.7 (H^b)			4.1 (H^b)		
	1.2 (H^c)			1.4 (H^c)			1.0 (H^c)		
31a[e]	0.7 (H^a)	1000	−4.0	1.0 (H^a)	24	−1.9	1.5 (H^a)	2500[a]	−4.6
	1.0 (H^b)			1.0 (H^b)			1.7 (H^b)		
32	4.7	> 10^5 [b]	–	5.0	200	−3.1	5.9	> 10^5 [b]	–

[a] Measured with **2b** as receptor. [b] Estimated value. [c] Measured at 25 °C. [d] Not measured yet. [e] Measured in $CDCl_3$/[D_6]acetone 1:1.

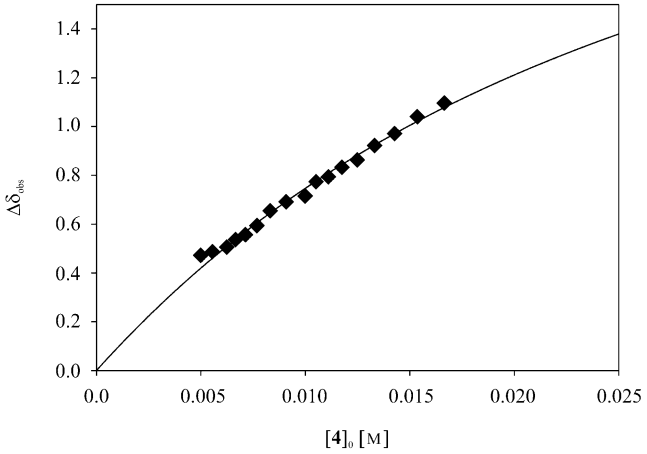


Figure 2. The plot of $\Delta\delta_{obs}$ of **23** as a function of the concentration of $[\mathbf{4}]_0$, where $[\mathbf{23}]_0 = 6.76 \times 10^{-3}$ M. Iterative fitting (bold line) affords $\Delta\delta_{max} = 2.9$ and the association constant $K_a = [\mathbf{23@4}]/[\mathbf{23}]\cdot[\mathbf{4}] = 43 \pm 4$ M^{-1}

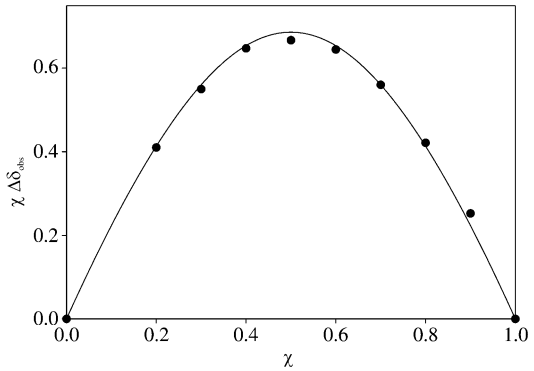


Figure 3. The Job plot for the complex **4@30** (Proton H^a of **30** is reported. Experimental data shown as black circles, the data as solid line is calculated with the parameters: $\Delta\delta_{max} = 3.46$ and $K_a = 414$ M^{-1})

the use of the HOSTEST program[34] for various host–guest stoichiometries (1:1, 2:1, 1:2) lead to reasonable fits for 1:1 stoichiometries only.

1,2,4,5-Tetracyanobenzene **32** (TCNB) forms a very stable bright yellow complex with **4.** A complexation-induced upfield shift of the TCNB protons of $\Delta\delta_{max} = 4.7$ ppm in the ^{1}H NMR spectrum in $CDCl_3$ was observed. The yellow color of the complex results from a charge-transfer (CT) absorption at $\lambda_{max} = 412$ nm ($\varepsilon = 1747$, $CHCl_3$). Since the complex **32@4** is too stable to determine the association constant K_a by an ordinary ^{1}H NMR titration experiment, we measured the heats of reaction and dilution in $CHCl_3$ at 25 °C by the use of an isothermal titration microcalorimeter[36] (Figure 4). From the analysis of the calorimetric data one can derive that besides the very stable (1:1) complex ($K_a = (14.3 \pm 0.9) \times 10^6$ M^{-1}, $\Delta G = -9.8 \pm 0.1$ kcal mol^{-1}, $\Delta H = -5.5 \pm 0.1$ kcal mol^{-1}, $\Delta S = 14.4 \pm 0.3$ cal mol^{-1} K^{-1}), a weaker (2:1) complex between **4** and **32** ($K_a = 43500 \pm 8800$ M^{-2} , $\Delta G = -6.3 \pm 0.1$ kcal mol^{-1}, $\Delta H = -5.67 \pm 0.1$ kcal mol^{-1}, $\Delta S = 2.2 \pm 0.8$ cal mol^{-1} K^{-1}) has to be formed.

The temperature-dependence of the ^{1}H NMR spectrum of the 1:1 mixture of **4** and **32** in $CDCl_3$ indicates a rapid exchange between the protons of the complexed and free **32.** At low temperature (−20 °C) a sharp signal at $\delta = 3.4$ ppm, assigned to complexed **32**, and the signals at $\delta = 4.3$, 4.1, 2.6, 2.4 and 2.2 ppm, assigned to the bridgehead CH and bridge CH_2 protons of complexed clip **4**, are consistent with the formation of a 1:1 complex **32@4**. The signal at $\delta = 3.4$ ppm shows broadening and a concomitant downfield shift to $\delta = 3.5$ ppm by raising the temperature from −20 °C to 25 °C (Figure 5a and b). This finding can be explained by either the dissociation or disproportionation of the 1:1 complex **32@4**.

[32@4] ⇌ **32** + **4** or **2** **[32@4]** ⇌ **[32@2·4]** + **32**

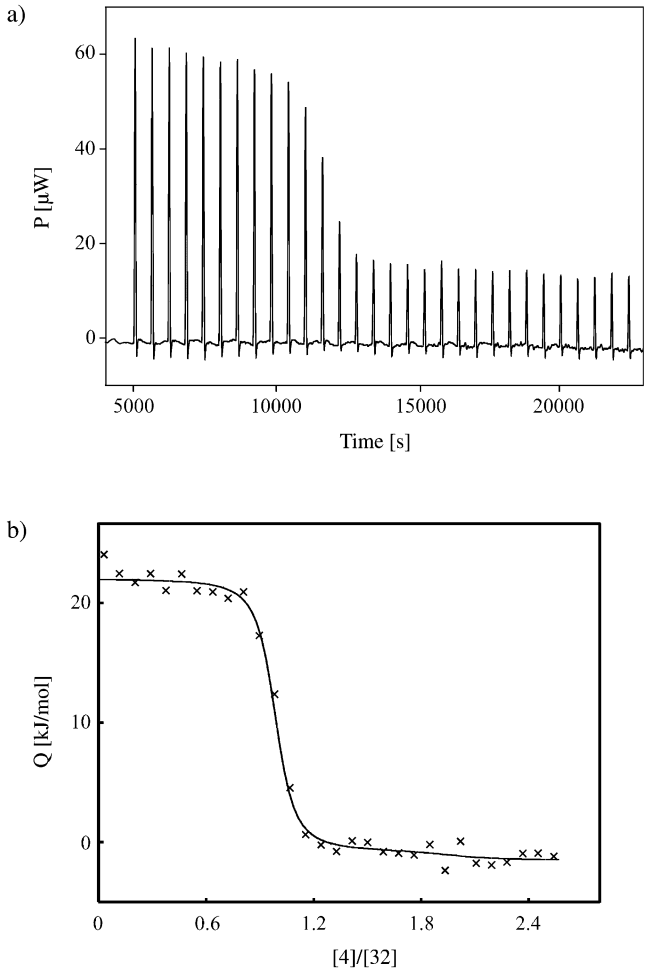


Figure 4. a) The plot of the experimental data: Measured power versus the time; b) The analysis of the experimental data: Heat of reaction versus concentration rate [**4**]/[**32**].

Consistent with the calorimetric analysis of the second process, the disproportionation, however, is evidently responsible for the exchange of the TCNB protons, as observed in the ^{1}H NMR spectrum. Further support for this explanation comes from the ^{1}H NMR spectrum of a 2:1 mixture of **4** and **32** at 25 °C. This shows a sharp signal for the protons of **32** at $\delta = 3.5$ ppm and averaged signals at $\delta = 4.1$, 2.5, 2.4 and 2.3 ppm for the bridgehead C*H* and bridge CH_2 protons of **4** (Figure 5c).[37] This indicates that there is, in this experiment, an exchange between the protons of complexed and free **4** (due to the excess of free **4**), and no exchange between the protons of complexed and free **32**, due to the absence of free **32**.

Discussion and Conclusion

The comparison of the receptor properties of the clips **3** and **4** with those of the benzene and naphthalene tweezers **1a** and **2a**[15–17] indicates that **3** and **4** are able to form complexes with sterically more demanding substrates than **1a** and **2a**. This is due to their more open topology caused by the reduction in number of methylene bridges from four to three. In Table 1 the data of complexation described for the clips **3** and **4** are compared with those of the naphthalene tweezers **2a** and **2b**. The substrates can be divided into two categories; one with "small" substituents such as the linear sp-hybridized cyano group or nonbranched alkyl groups, and the other one with sterically more demanding substituents such as the trigonal sp^2-hybridized nitro group conjugated to an aromatic ring. The substrates of the first category form complexes with clip **4** which are less stable than those with the naphthalene tweezers **2a** and **2b**, but more stable than those with the benzene tweezer **1a**. The complexes of **4** with the substrates of the second category are more stable than those of both the benzene and naphthalene tweezers. The clip **3** forms much weaker complexes with the substrates **23** and **26**–**32** than clip **4**, and no complexation is observed between **3** and **24** or **25** as substrates. Finally, in the UV/Vis spectrum of the colorless mixture of **3** and TCNB **32** in $CHCl_3$, no charge-transfer interaction can be detected, contrary to that observed in the UV/Vis spectrum of the yellow complex of **4** with **32** in $CHCl_3$ ($\lambda_{max} = 412$ nm, $\varepsilon = 1747$, CT). These findings can certainly be explained by the larger van der Waals contact surfaces of the naphthalene sidewalls in **4** compared to the smaller benzene systems in **3**. In the following, the discussion is focused on the

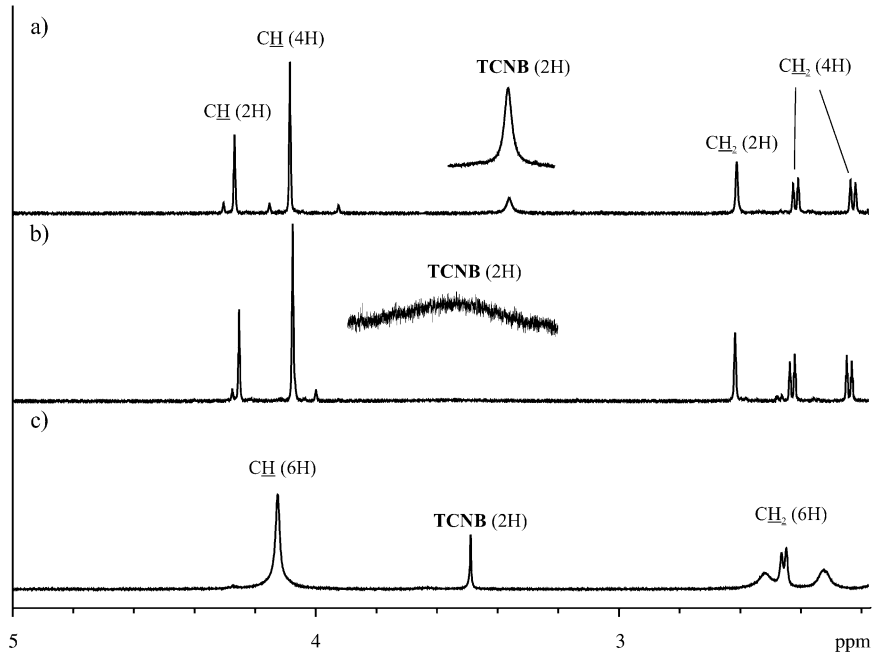


Figure 5. The temperature-dependent ^{1}H NMR spectra (500 MHz, $CDCl_3$) of **4** and **32** a) 1:1 mixture at −20 °C; b) 1:1 mixture at 25 °C; c) 2:1 mixture at 25 °C.

comparison of the receptor properties of **2a**, **2b** and **4**, and the structures of the corresponding complexes. Both receptors form highly stable complexes with TCNB **32**. The difference in the complex stabilities, which cannot be easily measured in these cases, is however not instructive for such a comparison. The weaker complexes of **2a** or **4** with *p*-, *o*-, and *m*-dicyanobenzene **23**–**25**, TCNQ **28**, Kosower salt **30**, and viologene **31** are better suited for this purpose. The complexes of **4** with **23**–**25**, **28**, **30** and **31** are less stable than those of **2a** by $\Delta\Delta G = 0.4 - 1.3$ kcal mol^{-1}. In the case of *p*-dinitrobenzene **26** as substrate, the complex of **4** is slightly more stable than that of tweezer **2a** by $\Delta\Delta G = -0.2$ kcal mol^{-1}. No complex formation could be detected between **2b** and fluorodinitrobenzene **27** and the fluorylidene derivative **29** within the limits of NMR detection, whereas both substrates form relatively stable complexes with **4**.

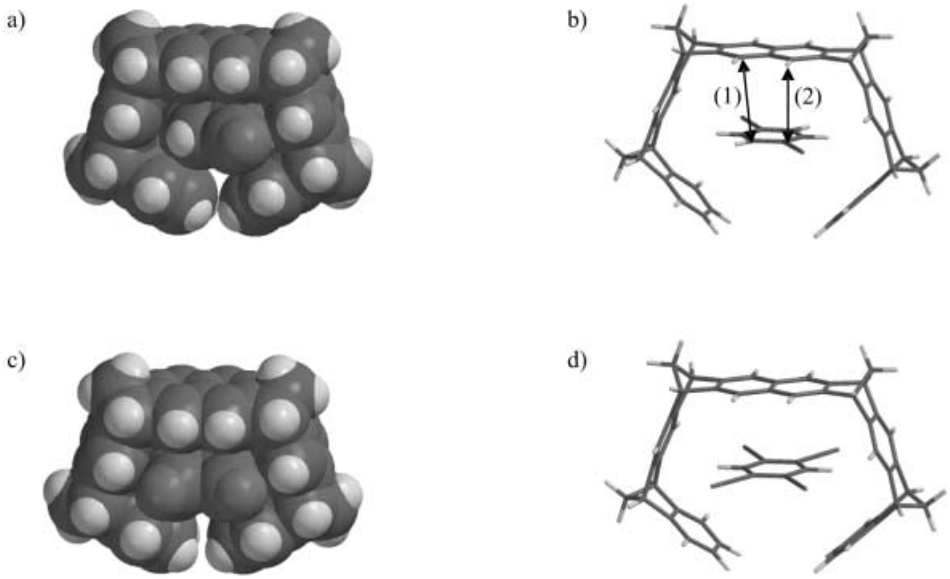


Figure 6. Comparison of experimentally determined and calculated structures of the complexes **23@2a**: a) X-ray (ref. [16]) b) MMFF94 (ref. [38]) the distances (1) and (2) are 356, 361 (X-ray), 387, 385 (MMFF94), and 431, 441 pm (PM3) and **32@2a**; c) X-ray; d) MMFF94. The distance between the cyano-substituted C-atom of **32** and naphthalene-C-atom of **2a** is 354 (x-ray), 376 (MMFF94), and 429 pm (PM3).

The maximum complexation-induced shifts ($\Delta\delta_{max}$) of the guest protons provide important information on the complex structures, as has been recently shown for the *p*-dicyanobenzene complex **23@2a**.[16, 17, 39] In its solid-state ^{1}H NMR spectrum two signals, at $\delta = 2.0$ and 5.6, were observed, which could be assigned to the pair-wise nonequivalent guest protons of **23** pointing either toward the opposite benzene rings adjacent to the central naphthalene spacer unit, or out of the cavity ($\Delta\delta_{max} = 5.8$ and 2.0 ppm, respectively). In the ^{1}H NMR spectrum in $CDCl_3$ only one signal at $\delta = 3.5$ ppm ($\Delta\delta_{max} = 4.3$ ppm) is observed for these protons, indicating that in solution the exchange of the nonequivalent protons, caused by mutual dissociation–association and/or rotation of the guest molecule inside the tweezer cavity, is fast with respect to the NMR time scale. The chemical shifts of the protons of **23**, calculated by quantum-chemical ab initio methods ($\delta_{calcd} = 2.5$ and 5.5), for the complex **23@2a** (isolated in the gas phase), are in very good agreement with the experimental solid-state data.[17, 39]

In this study simple force-field calculations, instead of the more extensive time-consuming quantum-chemical methods, were employed to calculate the complex structures and correlate them with the measured ^{1}H NMR data qualitatively. Quantitative ab initio calculations are in progress.[40] Since there are, hitherto, no X-ray data of the complexes with clip **4** as receptor available, we calibrated the force-field calculations with the known single-crystal structures of the complexes **23@2a** and **32@2a**. With the MMFF94 force field included in SPARTAN 02[38] we found reasonably good agreement between the calculated and experimentally determined structures (Figure 6). In the calculated structures, the distances between the central naphthalene spacer unit of the receptor and the benzene ring of the substrate are slightly larger (by about 10%, 22–31 pm) than those determined experimentally. In the complex structures calculated by the semiempirical PM3 method these deviation are larger (about 20%, 75 pm). In the PM3 calculations the repulsive van der Waals interactions between the host and guest arene units are, apparently, more overestimated than in the force-field calculation.

The complexes of clip **4** are conformationally more flexible than those of the tweezers **1a** and **2a**, due to the more open topology of the clip molecule. For the TCNB complex **32@4** two conformers are found, the conformer with the four cyano groups of **32** pointing out of the clip cavity is calculated to be more stable by 12.4 kcal mol^{-1} than the other with the two hydrogen atoms of **32** pointing out of the clip cavity (Figure 7a). The result of the calculation, that is, that the two hydrogen atoms of complexed **32** are nonequivalent in the ground-state conformation, seems to be contradictory to the finding of only one ^{1}H NMR signal for **32** in the complex **32@4**. This would be in better agreement with the high-energy conformation of **32@4**, with the two hydrogen atoms of **32** being equivalent. Preliminary temperature-dependent ^{1}H NMR measurements of **32@4** in [D_8]toluene showed, however, that at $-105\,^\circ$C the signal of **32** is split into two signals at $\delta = 2.9$ and 4.4 ppm. This provides evidence for the calculated low-energy conformation indeed being the ground state of **32@4**. The observation of one ^{1}H NMR signal of **32** at room temperature can be explained by an exchange of the positions of the two TCNB protons. This is caused by rotation of the TCNB molecule inside the clip cavity and/or mutual dissociation–association processes, which are rapid on the NMR time scale, so that only one averaged signal is observed. To date there is, however, no reasonable proposal for the structure of the 2:1 complex between clip **4** and TCNB **32**, as

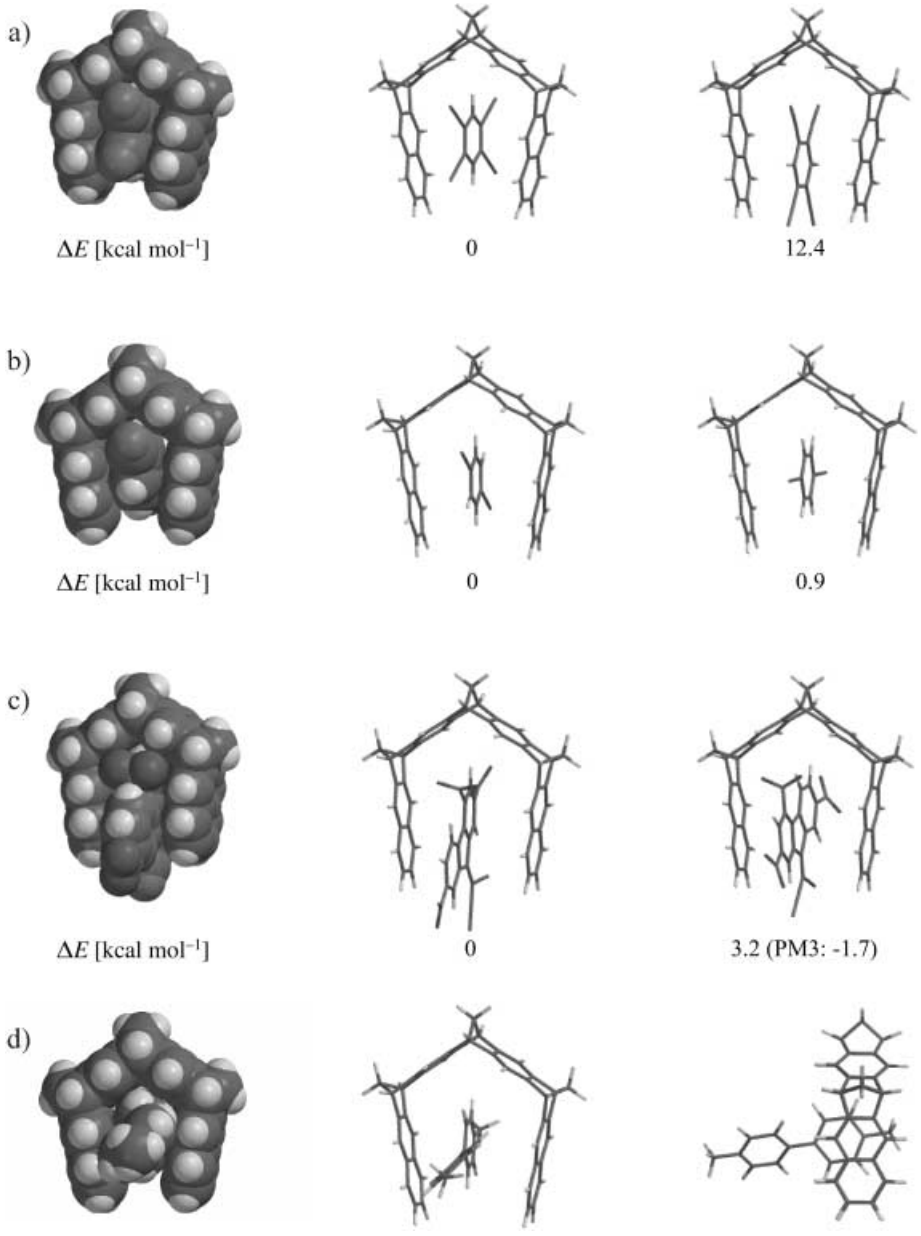


Figure 7. Structures and relative energies (ΔE) of the conformers of a) **32@4**; b) **23@4**; c) **29@4**; and d) **31b@4** calculated by force-field MMFF94 (ref [38])

indicated by the calorimetric measurements. According to Monte-Carlo simulations (MacroModel 7.0, AMBER*) the 2:1 complex consists of the structure of the 1:1 complex, in which one naphthalene sidewall is sandwiched by a second clip molecule **4**.

According to the calculations, each of the complexes of **4** with the dicyanobenzene derivatives **23**–**25** as guest molecules consists of a fast equilibrium between two or three noncovalently bonded conformers, as is shown for the example of **23@4** (Figure 7b; for the structures of **24@4** and **25@4** see Figure 2 in the Supporting Information). This explains that the complexation-induced ^{1}H NMR shifts of the nonequivalent guest protons are of similar size in each complex. However, the question remains open why, in the case of **25@4**, the complexation-induced shifts of the guest protons are significantly smaller than those in the other two complexes (**23@4** and **24@4**).

Only one conformer is found in the calculation of the 1,4-dinitrobenzene complex **26@4**, whereas the fluorodinitrobenzene complex **27@4** is calculated to consist of an equilibrium between two conformers (see Figure 4 in the Supporting Information). The comparison of the calculated and the measured ^{1}H NMR shifts is particularly instructive in the case of **29@4**. In this case the complexation-induced ^{1}H NMR shifts show that the mononitro-substituted benzene ring is preferentially positioned inside the clip cavity, contrary to the force-field calculations, which favor the conformation with the dinitro-substituted benzene ring inside the clip cavity. This is, however, in agreement with the semiempirical PM3 calculation (Figure 7c).

For the complexes of the cationic guests **30@4** (see Figure 3 in the Supporting Information) and **31b@4**, each calculation only leads to one conformer in which the positively charged nitrogen atom is positioned inside the cavity. The finding of only two signals for the protons H^a and H^b of **31a** in complex **31a@4**, and their relatively small complexation-induced shifts, indicate that, on the NMR time scale, the clip molecule moves back and forth from one to the other pyridinium ring of **31** fast. Only averaged signals of the complexed and uncomplexed pyridinium ring are therefore observed.

The clip molecules **3** and **4** serve as receptors for electron-deficient neutral and cationic substrates, comparable to the molecular tweezers **1** and **2**. Neither complex formation between these receptors and electron-rich arenes such as benzene and naphthalene or anionic substrates, nor association between parent benzene or naphthalene and electron-deficient guest molecules (e.g. **23**–**32**) can be observed within the limits of ^{1}H NMR detection in $CDCl_3$ solution. These findings can be explained by the electrostatic potential surface (EPS) calculated by means of quantum-chemical methods.[38] In agreement with analogous calculations for the molecular tweezers **1** and **2**,[20] the EPS of **3** and **4** is calculated with various quantum-chemical methods to be highly negative on their concave faces, whereas the EPS on their convex faces is similar to that of alkyl-substituted arenes (Figure 8). Accord-

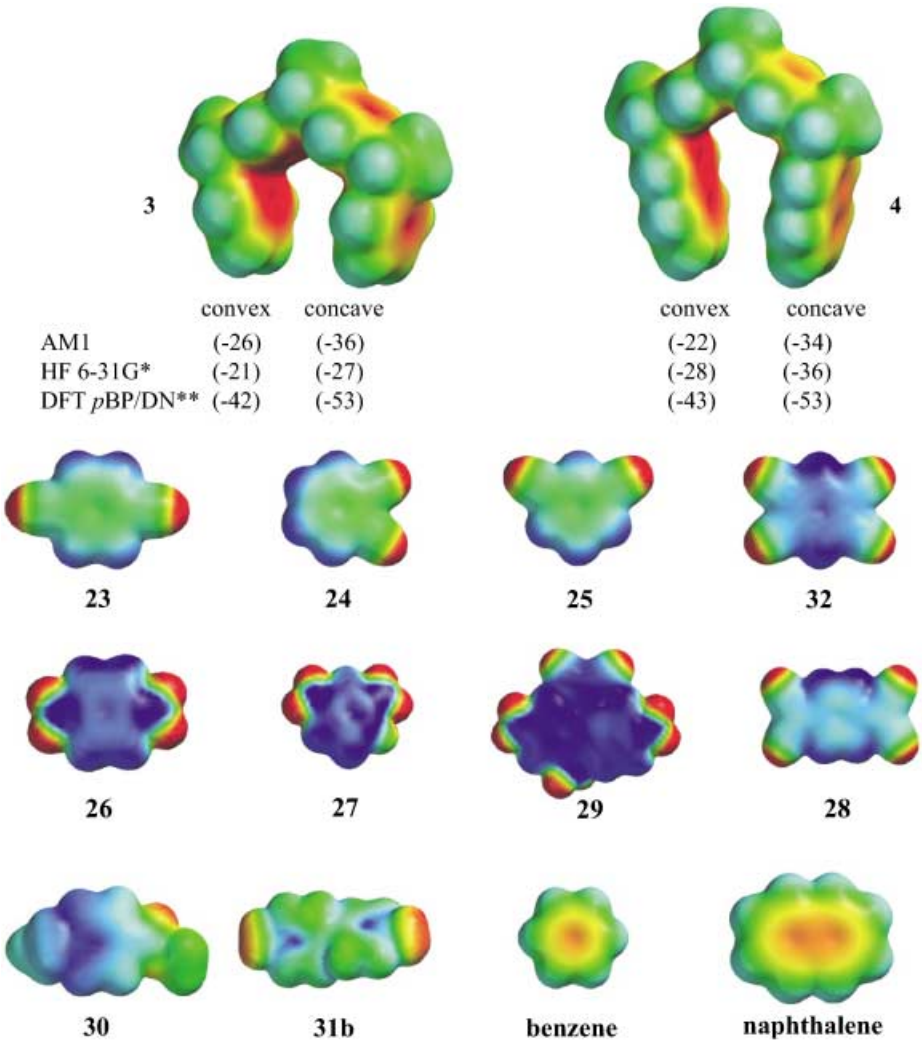


Figure 8. EPSs of clips **3**, **4** and substrates **23**–**30**, **31b**, **32**, benzene and naphthalene calculated by AM1 are depicted. The color code spans from −25 (red) to +25 kcal mol^{-1} (blue) in the case of the neutral compounds and from +6 (red) to +121 (blue) and from +138 to +183 kcal mol^{-1} in the case of cation **30** and dication **31b**, respectively. The most negative molecular electrostatic potentials (MEPs) on the concave and convex face of **3** and **4** calculated with AM1, ab initio, and DFT are given in parenthesis.

ing to these quantum-chemical calculations this seems to be a general phenomenon of nonconjugated π systems with convex–concave topology. The results of the calculations are largely independent of the applied theoretical methods, so that calculations with the inexpensive AM1 method give similar results as those with more expensive ab initio or DFT methods.[38] When EPS calculations were performed for the aromatic substrates, which form complexes with **3** and **4**, the complementary nature of the substrate and receptor EPSs becomes evident (Figure 8). This suggested that the receptor–substrate interactions reported here for the clips **3** and **4** are predominantly of electrostatic nature, comparable to those of tweezers **1** and **2**.

Experimental Section

IR: Bio-Rad FTS 135. UV: Varian Cary 300 Bio. ^{1}H-NMR, ^{13}C-NMR, DEPT H, H-COSY, C, H-COSY, NOESY, HMQC, HMBC: Bruker DRX 500. ^{1}H-NMR titration experiments: Varian Gemini XL 200 and Bruker DRX 500; 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: Fison Instruments VG ProSpec 3000 (70 eV). All melting points are uncorrected. Thin-layer chromatography (tlc): Polygram SIL G/UV$_{254}$ 0.2 mm silica gel with fluorescent indicator. Column chromatography: silica gel 0.063–0.2 mm. All solvents were distilled prior to use. Ampoules were sealed in vacuo after three freeze (2-propanol/dry ice) and thaw cycles using argon as an inert gas.

5,6,6a,7,7a,8,9,14,15,15a,16,16a,17,18-Tetracosahydro-5,18:7,16:9,14-trimethanoheptacene (10): A solution of diene **8**[41] (375 mg, 2.23 mmol), bisdienophile **9** (102 mg, 1.11 mmol), and anhydrous triethylamine (three drops) in anhydrous toluene (1.7 mL) was heated to 170 °C for three days in a sealed ampoule. The reaction mixture was cooled overnight in a refrigerator. The precipitated product was filtered off and washed thoroughly with cold hexane and dried in vacuo. The colorless product **10** (136 mg, 0.32 mmol, 29 %) was used for recording the spectral data and the synthesis of **3** without further purification. tlc: $R_f = 0.51$ (cyclohexane/ethyl acetate 10:1); m.p. 229 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.29$ (bs, 6H; 6a-, 7a-, 15a-, 16a-H, 20-H$_2$), 1.57 (s, 2H; 7-, 16-H), 1.84–2.21 (m, 12H; 6-, 8-, 15-, 17-, 19-, 21-H$_2$), 3.51 (s, 4H; 5-, 9-, 14-, 18-H), 6.82 (m, 4H; 2-, 3-, 11-, 12-H), 7.09 ppm (m, 4H; 1-, 4-, 10-, 13-H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 29.22$ (t; C-6, C-8, C-15, C-17), 30.42 (t; C-20), 42.40 (d; C-6a, C-7a, C-15a, C-16a), 53.54 (d; C-5, C-9, C-14, C-18), 54.59 (d; C-7, -16), 66.50 (t; C-19, C-21), 120.49 (d; C-1, C-4, C-10, C-13), 123.75 (d; C-2, C-3, C-11, C-12), 147.00 (s; C-5a, C-8a, C-14a, C-17a), 152.33 ppm (s; C-4a, C-9a, C-13a, C-18a); IR (KBr): $\tilde{\nu} = 3068$ (CH), 2978 (CH$_2$), 2830 (CH), 1692 (C=C), 1574 (C=C), 1454 (CH), 751 cm^{-1} (CH); UV/Vis ($CHCl_3$): λ_{max} (log ε) = 240 (3.50), 272 nm (3.39); MS (70 eV): *m*/*z* (%): 428 (100) [M^+], 194 (48) [$M^+ - C_{18}H_{18}$], 116 (79) [$M^+ - C_{24}H_{24}$]; HR-MS (70 eV): calcd ($C_{33}H_{32}$) 428.250401; found 428.25038.

5,7,9,14,16,18-Hexahydro-5,18:7,16:9,14-trimethanoheptacene (3): DDQ (275 mg, 1.21 mmol) was added to a solution of **10** (100 mg, 0.23 mmol) in anhydrous toluene (7 mL). The vigorously stirred mixture was immediately placed into an oil bath preheated to 110 °C and kept at 110 °C for two hours. The reaction mixture was allowed to cool down to 50 °C. The excess DDQ was converted to $DDQH_2$ by reaction with added 1, 4-cyclohexadiene (0.2 mL). After stirring for 15 min at 50 °C, the mixture was filtered and the filtrate was concentrated in vacuo. Purification of the crude product by column chromatography (silica gel, cyclo-hexane/ethyl acetate 10:1) followed by recrystallization from ethanol yielded **3** as a colorless solid (57 mg, 0.13 mmol, 59 %). $R_f = 0.51$ (cyclohexane/ethyl acetate 10:1) ; m.p. 226 °C ; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.44$ (s, 6H; 19-, 20-, 21-H$_2$), 3.99 (s, 2H; 7-, 16-H), 4.07 (s, 4H; 5-, 9-, 14-, 18-H), 6.77 (m, 4H; 2-, 3-, 11-, 12-H), 7.10 (m, 4H; 1-, 4-, 10-, 13-H), 7.11 ppm (s, 4H; 6-, 8-, 15-, 17-H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 51.22/51.25$ (d; C-5, C-7, C-9, C-14, C-16, C-18), 68.83 (t; C-19, C-21), 69.94 (t; C-20), 116.06 (d; C-6, C-8, C-15, C-17), 121.29 (d; C-1, C-4, C-10, C-13), 124.80 (d; C-2, C-3, C-11, C-12), 147.24 (s; C-5a, C-8a, C-14a, C-17a), 147.70 (s; C-6a, C-7a, C-15a,

C-16a), 150.70 ppm (s; C-4a, C-9a, C-13a, C-18a); IR (KBr): $\tilde{\nu}=3067$ (CH), 2968 (CH_2), 2858 (CH), 1560 (C=C), 1458/1438 (CH), 800 (CH), 751 cm^{-1} (CH); UV/Vis ($CHCl_3$): λ_{max} (log ε) = 241 (4.02), 282 (3.89), 299 nm (3.98); MS (70 eV): *m/z* (%): 420 (100) [M^+], 405 (19) [$M^+ - CH_3$], 203 (12) [$M^+ - C_{17}H_{17}$]; HR-MS (70 eV): calcd ($C_{33}H_{24}$) 420.187801; found 420.187385.

***trans/cis*-2,3-Bis(chlormethyl)-1,4-methano-1,2,3,4-tetrahydroanthracene (15)**: Powdered sodium iodide (77.1 g) was added in one portion under argon to a stirred solution of tetrabromo-*o*-xylene **11** (31.65 g, 75 mmol) and dienophile **13**[29] (5.7 g, 30 mmol) in anhydrous DMF (300 mL) at 65 °C. The mixture was stirred for 16 h, and then poured into ice water (600 mL). Saturated aqueous $NaHSO_3$ was added to the brownish mixture until its color turned to light yellow. The mixture was extracted with dichloromethane (300 mL). The separated organic phase was washed with saturated aqueous $NaHCO_3$, water, and dried over anhydrous $MgSO_4$. After removal of the solvent the byproduct was removed by distillation in vacuo at 120 °C/1 mbar. The residue was purified by column chromatography (silica gel, cyclohexane/ethyl acetate 10:1) yielding **15** as a light-brown colored oily product (5.84 g, 20 mmol, 67%). tlc: $R_f=0.69$ (cyclohexane/ethyl acetate 10:1); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=1.5$ (q; 11-H), 1.95 (dd, 2H; 13-H), 2.3 (sextett, 1H; 6-H), 3.62 (m, 2H; 8-H), 2.70/3.28/3.42 (s/q/t, 2H; 7-, 10-H), 3.67 (m, 2H; 9-H), 7.45 (d, 2H; 2-, 3-H), 7.60 (s, 1H; 5-H), 7.70 (s, 1H; 12-H), 7.78 ppm (m, 2H; 1-, 4-H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta=45.36$ (t; C-13), 46.52 (d; C-7), 46.92 (d; C-10), 47.98 (t; C-8, C-9), 48.78 (d; C-6), 50.02 (d; C-11), 118.71 (d; C-5), 121.50 (d; C-12), 125.28/125.37 (d; C-2/C-3), 127.77/127.81 (d; C-1/C-4), 132.56 (s; C-4a), 133.04 (s; C-12a), 141.65 (s; C-5a), 145.76 (s; C-11a).

2,3-Bis-exo-methylene-1,4-methano-1,2,3,4-tetrahydroanthracene (19): Potassium hydroxide (3 g, 54 mmol) was added in portions to a solution of [18]crown-6 (204 mg, 0.77 mmol) and **15** (531mg, 1.84 mmol) in tetrahydrofuran (25 mL) under argon at 0 °C . The mixture was stirred for 30 min at 0 °C and 36 h at 85 °C. After cooling to room temperature the mixture was poured into ice water (30 mL). The aqueous phase was extracted with ether (2×30 mL), the combined organic phases were washed with water and dried over anhydrous $MgSO_4$. After removal of the ether the crude product was purified by column chromatography (silica gel, hexane/chloroform 4:1) yielding diene **19** as a colorless solid (297 mg, 1.36 mmol, 74%). tlc: $R_f=0.59$ (*n*-hexane/$CHCl_3$ 4:1); m.p. 117 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=2.10$ (dd, 2H; ^2J(13a-H, 13i-H) = 9 Hz, ^3J(13a-H, 11-H) = 1.5 Hz, 13a-, 13i-H), 4.00 (s, 2H; 6-, 11-H), 5.10 (s, 2H; 8a-, 9a-H), 5.22 (s, 2H; 8i-, 9i-H), 7.38 (m, 2H; ^3J(3-H, 4-H) = 3 Hz, 2-, 3-H), 7.60 (s, 2H; 5-, 12-H), 7.72 ppm (m, 2H; ^3J(1-H, 2-H) = 3 Hz, 1-, 4-H); ^{13}C NMR (126 MHz,$CDCl_3$): $\delta=50.62$ (t; C-13), 52.23 (d; C-6, C-11), 102.43 (t; C-8, C-9), 118.83 (d; C-5, C-12), 125.11 (d; C-2, C-3), 127.73 (d; C-1, C-4), 132.93 (s; C-4a, C-12a), 144.75 (s; C-7, C-10), 148.60 ppm (s; C-5a, C-11a); IR (KBr): $\tilde{\nu}=3059$ (CH), 2990 (CH), 2933 (CH_2), 1504 (C=C), 900 (CH), 757 cm^{-1} (CH); UV/Vis ($CHCl_3$): λ_{max} (log ε) = 259 nm (4.00), 308 nm (3.06), 323 nm (3.10); MS (70 eV): m/z (%): 218 (100) [M^+], 203 (18) [$M^+ - CH_3$], 202 (16) [$M^+ - CH_4$], 165 (26) [$M^+ - C_4H_5$]; HR-MS (70 eV): calcd ($C_{17}H_{14}$) 218.109551; found 218.1096.

6,7,7a,8,8a,9,10,17,19,21-Tetracosahydro-6,21:8,19:10,17-trimethanononacene (20): A solution of diene **19** (375 mg, 1.72 mmol), bisdienophile **9** (73 mg, 0.79 mmol), and anhydrous triethylamine (three drops) in anhydrous toluene (3.5 mL) was heated to 170 °C for three days in a sealed ampoule. The reaction mixture was cooled over night in a refrigerator. The precipitated product was filtered off and washed thoroughly with cold toluene and dried *in vacuo*. The colorless product **20** (122 mg, 0.24 mmol, 28%) was used without further purification. At room temperature **20** is unstable and decomposes within 24 h. Therefore, **20** has to be used for the next step immediately. It can be stored for a short period of time in the refrigerator without decomposing. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=1.25$ (m, 6H; 7a-, 8a-, 18a-, 19a-, 24-H) , 1.55 (m, 2H; 8-, 19-H), 1.89 (m, 4H; 7-, 9-, 18-, 20-H), 2.12 – 2.25 (m, 8H; 7′-, 9′-, 18′-, 20′-, 23-, 25-H), 3.60 (s, 4H; 6-, 10-, 17-, 21-H), 7.28 (m, 4H; 1-, 4-, 12-, 15-H), 7.40 (s, 4H; 5-, 11-, 16-, 22-H), 7.60 ppm (m, 4H; 2-, 3-, 13-, 14-H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta=$ 28.97 (t; C-7, C-9, C-18, C-20), 30.50 (t; C-24), 42.26 (d; C-7a, C-8a, C-18a, C-19a), 52.82 (d; C-8, C-19), 54.54 (d; C-6, C-10, C-17, C-21), 62.97 (t; C-23, C-25), 118.04 (d; C-2, C-3, C-13, C-14), 124.78 (d; C-1, C-4, C-12, C-15) , 127.41 (d; C-5, C-11, C-16, C-22), 132.00 (s; C-4a, C-11a, C-15a, C-22a), 146.35 (s; C-6a, C-9a, C-17a, C-20a), 149.27 (s; C-5a, C-10a, C-16a, C-21a).

6,8,10,17,19,21-Hexahydro-6,21:8,19:10,17-trimethanononacene (4): DDQ (280 mg, 1.23 mmol) was added to a solution of **20** (79 mg, 0.15 mmol) in anhydrous toluene (10 mL). The vigorously stirred mixture was immediately placed into an oil bath preheated to 110 °C and kept at 110 °C for three hours. The reaction mixture was allowed to cool down to 50 °C. The excess DDQ was converted to $DDQH_2$ by reaction with added 1,4-cyclohexadiene (0.2 mL). After stirring for 15 min at 50 °C the mixture was filtered and the filtrate was concentrated in vacuo. Purification of the crude product by column chromatography (silica gel, *n*-hexane/chloroform 4:1) yielded **4** as a colorless solid (35 mg, 0.07 mmol, 47%). tlc: $R_f=0.48$ (*n*-hexane/$CHCl_3$ 4:1); m.p. > 300 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=2.43$ (m, 6H; s, 2H; 24-H_2; superimposed with an AB spectrum: d, 4H; ^2J(23a-H, 23i-H) = ^2J(25a-H, 25i-H) = 8 Hz, 23-H_2, 25-H_2;), 4.00 (s, 2H; 8-, 19-H), 4.17 (s, 4H; 6-, 10-, 17-, 21-H), 7.13 (s, 4H; 7-, 9-, 18-, 20-H), 7.15 (m, 4H; 2-, 3-, 13-, 14-H), 7.40 (s, 4H; 5-, 11-, 16-, 22-H), 7.44 ppm (m, 4H; 1-, 4-, 12-, 15-H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta=51.10$ (d; C-6, C-10, C-17, C-21), 51.64 (d; C-8, C-19), 66.59 (t; C-23, C-25), 70.29 (t; C-24), 116.42 (d; C-7, C-9, C-18, C-20), 119.44 (d; C-1, C-4, C-12, C-15), 125.40 (d; C-2, C-3, C-13, C-14), 127.90 (d; C-5, C-11, C-16, C-22), 132.34 (s; C-6a, C-9a, C-17a, C-20a), 146.68 (s; C-4a, C-11a, C-15a, C-22a), 147.89 (s; C-5a, C-10a, C-16a, C-21a), 148.39 ppm (s; C-7a, C-8a, C-18a, C-19a); IR (KBr): $\tilde{\nu}=3057$ (CH), 2972 (CH_2), 2936 (CH_2), 2864 (CH), 1609 (C=C), 1504 (C=C), 1454 (CH_2), 1427(CH_2), 888 (CH), 748 ppm (CH); UV/Vis ($CHCl_3$): λ_{max} (log ε) = 250 (4.19), 279 (4.09), 310 (3.57), 324 (3.51); MS (70 eV): *m/z* (%): 520 (90) [M^+], 505 (12) [$M^+ - CH_3$], 260 (13) [$M^+ - C_{20}H_{20}$], 28 (52) [$M^+ - C_{39}H_{24}$]; HR-MS (70 eV): calcd. ($C_{41}H_{28}$) 520.2191; found 520.2191.

Determination of K_a: ^{1}H NMR titration method: Receptor R and substrate S are in equilibrium with the 1:1 complex RS (R + S ⇄ RS). The association constant K_a is then defined by Equation (1). $[R]_0$ and $[S]_0$ are the starting concentrations of the receptor and the substrate, respectively.

$$K_a=\frac{[RS]}{[R][S]}=\frac{[RS]}{([R]_0-[RS])([S]_0-[RS])} \quad (1)$$

The observed chemical shift δ_{obs} of the substrate in the ^{1}H NMR spectrum is an averaged value between free (δ_0) and complexed substrate (δ_{RS}), assuming that the exchange is fast on the NMR time scale [Eq. (2)].

$$\delta_{obs}=\frac{[S]}{[S]+[RS]}\delta_0+\frac{[RS]}{[S]+[RS]}\delta_{RS} \quad (2)$$

Combination of Equations (1) and (2) and the use of differences in chemical shift ($\Delta\delta=\delta_0-\delta_{obs}$; $\Delta\delta_{max}=\delta_0-\delta_{RS}$) leads to Equation (3).

$$\Delta\delta=\frac{\Delta\delta_{max}}{[S]_0}\cdot\frac{1}{2}\left([R]_0+[S]_0+\frac{1}{K_a}\right)-\sqrt{\frac{1}{4}\cdot\left([R]_0+[S]_0+\frac{1}{K_a}\right)^2-[R]_0\cdot[S]_0} \quad (3)$$

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 0.6 mL of a solution 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 ^{1}H NMR spectrum (500 MHz, 25 °C for R = **3** and 200 MHz, 24 °C for R = **4**) of this mixture. Successive addition of further solution containing $[S]_0$ leads to a dilution of $[R]_0$ in the mixture while $[S]_0$ is kept constant. Measurement of the chemical shift of the substrate dependent on the concentration $[R]_0$ afforded the data pairs $\Delta\delta$ and $[R]_0$. Fitting of these data to the 1:1 binding isotherm by iterative methods[34] delivered the parameters K_a and $\Delta\delta_{max}$.

In the case of substrates possessing more than one kind of nonequivalent protons, the determination of the association constants K_a sometimes lead to different values of K_a. This may result from increasing errors caused by decreasing $\Delta\delta_{max}$ values. To minimize such errors the association constants K_a were determined for that proton of the substrate S displaying the largest value for $\Delta\delta_{max}$. The $\Delta\delta_{max}$ values of the other kind of substrate protons are calculated by the use of Equation (5); which is derived from Equation (4).

$$[RS]=[S]_0\frac{\Delta\delta_1}{\Delta\delta_{1,max}}=[S]_0\frac{\Delta\delta_2}{\Delta\delta_{2,max}}=[S]_0\frac{\Delta\delta_n}{\Delta\delta_{n,max}} \quad (4)$$

$$\Rightarrow\Delta\delta_{n,max}=\Delta\delta_n\frac{\Delta\delta_1}{\Delta\delta_{1,max}} \quad (5)$$

From the corresponding relationship between the concentrations of the receptor $[R]_0$ and the complex [RS], the maximum complexation-induced shifts $\Delta\delta_{R,max}$ for the protons of the receptor R can be calculated by the use of Equation (7), which is derived from Equation (6)..

$$[RS] = [S]_0 \frac{\Delta\delta_1^S}{\Delta\delta_{1,max}^S} = [R]_0 \frac{\Delta\delta_1^R}{\Delta\delta_{1,max}^R} \quad (6)$$

$$\Rightarrow \Delta\delta_{1,max}^R = \frac{[R]_0}{[S]_0} \Delta\delta_1^R \frac{\Delta\delta_{1,max}^S}{\Delta\delta_1^S} \quad (7)$$

Crystal structure determinations

Complexes of 3 with water and ethanol: $C_{33}H_{24} \cdot C_2H_6O \cdot H_2O$, crystal dimensions $0.27 \times 0.22 \times 0.17$ mm^3, crystal color: yellow; measured on a Siemens P4 diffractometer with $Mo_{K\alpha}$-radiation. $T = 293$ K. Cell dimensions $a = 8.651(3)$, $b = 29.017(5)$, $c = 18.077(2)$ Å, $\beta = 91.87(2)^\circ$, $V = 4535(2)$ Å^3, monoclinic crystal system, $Z = 6$, $\rho_{calcd} = 0.993$ g cm^{-3}, space group $P2_1/m$, due to high disorder of the water and ethanol in the cavities, the refinement was unsatisfactory.

Complexes of 3 with ethanol: $C_{33}H_{24} \cdot C_2H_6O$, crystal dimensions $0.42 \times 0.37 \times 0.22$ mm^3, crystal color: yellow, measured on a Siemens SMART-CCD diffractometer with $Mo_{K\alpha}$-radiation. $T = 203$ K. Cell dimensions $a = 8.843(3)$, $b = 13.465(5)$, $c = 21.341(8)$ Å, $\beta = 97.698(7)^\circ$, $V = 2518.2(16)$ Å^3, monoclinic crystal system, $Z = 4$, $\rho_{calcd} = 1.231$ g cm^{-3}, $\mu = 0.072$ mm^{-1}, space group $P2_1/n$, data collection of 32067 intensities, 6275 independent ($R_{merg} = 0.0256$, $4.45^\circ = \Theta = 28.36^\circ$), 5245 observed [$F_o \geq 4\sigma(F)$], absorption correction with Bruker AXS SADABS program multiscan V2.03: R_{merg} before/after: 0.0987/0.0354, max/min transmission 1.00/0.92; structure solution with direct methods (SHELXS) and refinement on F^2 (SHELXTL 5.10) (334 parameters). The hydrogen atom positions were calculated and refined as riding groups with the 1.2 fold of the corresponding C atoms. $R1 = 0.0589$, $wR2$ (all data) $= 0.1623$, $w^{-1} = \sigma^2(F_o^2) + (0.0953P)^2 + 0.595P$, where $P = [\max(F_o^2) + (2F_c^2)]/3$, maximum residual electron density 0.549 e Å^{-3}. Ethanol oxygen atom O1 disordered over two sites with occupancies 0.5.

CCDC-218210 and CCDC-218211 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.uk).

Acknowledgement

This work was supported by the Deutsche Forschungsgemeinschaft (Sonderforschungsbereich SFB 452) and the Fonds der Chemischen Industrie. We thank Dieter Bläser for performing the X-ray measurements, Professor Monika Mazik, Dr. Torsten Schaller, Dr. Wolfgang Radunz, Willi Sicking, and Kerstin Antepoth for their assistance with the calorimetric measurements, Job-plot analyses, the HOSTEST calculations, and Professor Craig Wilcox for providing us access to the HOSTEST program.

[1] J. M. Lehn, *Supramolecular Chemistry. Concepts and Perspectives*, VCH, Weinheim, **1995**; H.-J. Schneider, A. Yatsimirsky, *Principles and Methods in Supramolecular Chemistry*, VCH, Weinheim, **2000**.

[2] J. L. Atwood, J. E. D. Davies, D. D. MacNicol, F. Vögtle, K. S. Suslick, *Comprehensive Supramolecular Chemistry*, Elsevier, Oxford, **1996**; D. Philp, J. F. Stoddart, *Angew. Chem.* **1996**, *108*, 1243 – 1286; *Angew. Chem. Int. Ed.* **1996**, *35*, 1155 – 1196;J. L. Atwood, J. W. Steed, *Supramolecular Chemistry*, VCH, Weinheim, **2000**.

[3] G. A. Jeffrey, W. Saenger, *Hydrogen Bonding In Biological Structures*, Springer, Berlin, **1991**; M. M. Conn, G. Deslongchamps, J. Demendoza, J. Rebek, *J. Am. Chem. Soc.* **1993**, *115*, 3548 – 3557; G. A. Jeffrey, *An Introduction of Hydrogen Bonding*, Oxford University Press, New York, **1997**; Y. L. Cho, D. M. Rudkevich, A. Shivanyuk, K. Rissanen, J. Rebek, *Chem. Eur. J.* **2000**, *6*, 3788 – 3796; A. Shivanyuk, J. Rebek, *Chem. Commun.* **2001**, 2374 – 2375; L. J. Prins, D. N. Reinhoudt, P. Timmerman, *Angew. Chem.* **2001**, *113*, 2446 – 2492; *Angew. Chem. Int. Ed.* **2001**, *40*, 2383 – 2426.

[4] P. J. Smith, E. I. Kim, C. S. Wilcox, *Angew. Chem.* **1993**, *105*, 1728 – 1730; *Angew. Chem. Int. Ed.* **1993**, *32*, 1648 – 1650; T. H. Webb, C. S. Wilcox, *Chem. Soc. Rev.* **1993**, *22*, 383 – 395; E. Kim, S. Paliwal, C. S. Wilcox, *J. Am. Chem. Soc.* **1998**, *120*, 11192 – 11193; C. Raposo, C. S. Wilcox, *Tetrahedron Lett.* **1999**, *40*, 1285 – 1288.

[5] J. P. Gallivan, D. A. Dougherty, *J. Am. Chem. Soc.* **2000**, *122*, 870 – 874.

[6] A. Ben-Naim, *Hydrophobic Interactions*, Plenum, New York, **1980**; C. Tanford, *The Hydrophobic Effect, 2nd ed.*, Wiley, New York, **1980**; S. S. Yoon, W. C. Still, *J. Am. Chem. Soc.* **1993**, *115*, 823 – 824; L. F. Newcomb, S. H. Gellman, *J. Am. Chem. Soc.* **1994**, *116*, 4993 – 4994; L. F. Newcomb, T. S. Haque, S. H. Gellman, *J. Am. Chem. Soc.* **1995**, *117*, 6509 – 6519; S. H. Gellman, T. S. Haque, L. F. Newcomb, *Biophys. J.* **1996**, *71*, 3523 – 3525.

[7] C. A. Hunter, J. K. M. Sanders, *J. Am. Chem. Soc.* **1990**, *112*, 5525 – 5534; W. L. Jorgensen, D. L. Severance, *J. Am. Chem. Soc.* **1990**, *112*, 4768 – 1774; S. Paliwal, S. Geib, C. S. Wilcox, *J. Am. Chem. Soc.* **1994**, *116*, 4497 – 4498; C. Chipot, R. Jaffe, B. Maigret, D. A. Pearlman, P. A. Kollman, *J. Am. Chem. Soc.* **1996**, *118*, 11217 – 11224; G. A. Breault, C. A. Hunter, P. C. Mayers, *J. Am. Chem. Soc.* **1998**, *120*, 3402 – 3410; F. J. Carver, C. A. Hunter, E. M. Seward, *Chem. Commun.* **1998**, 775 – 776; H. Adams, C. A. Hunter, K. R. Lawson, J. Perkins, S. E. Spey, C. J. Urch, J. M. Sanderson, *Chem. Eur. J.* **2001**, *7*, 4863 – 4877; C. A. Hunter, K. R. Lawson, J. Perkins, C. J. Urch, *J. Chem. Soc. Perkin Trans. 2* **2001**, 651 – 669; F. J. Carver, C. A. Hunter, P. S. Jones, D. J. Livingstone, J. F. McCabe, E. M. Seward, P. Tiger, S. E. Spey, *Chem. Eur. J.* **2001**, *7*, 4854 – 4862; F. J. Carver, C. A. Hunter, D. J. Livingstone, J. F. McCabe, E. M. Seward, *Chem. Eur. J.* **2002**, *8*, 2848 – 2859; G. Chessari, C. A. Hunter, C. M. R. Low, M. J. Packer, J. G. Vinter, C. Zonta, *Chem. Eur. J.* **2002**, *8*, 2860 – 2867; M. O. Sinnokrot, E. F. Valeev, C. D. Sherrill, *J. Am. Chem. Soc.* **2002**, *124*, 10887 – 10893; most recent review: E. A. Meyer, R. K. Castellano, F. Diederich, *Angew. Chem.* **2003**, *115*, 1244 – 1287; *Angew. Chem. Int. Ed.* **2003**, *42*, 1210 – 1250.

[8] P. C. Kearney, L. S. Mizoue, R. A. Kumpf, J. E. Forman, A. McCurdy, D. A. Dougherty, *J. Am. Chem. Soc.* **1993**, *115*, 9907 – 9919; D. A. Dougherty, *Abstr. Pap. Am. Chem. Soc.* **1994**, *207*, 350-ORGN; S. Mecozzi, A. P. West, D. A. Dougherty, *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 10566 – 10571; S. Mecozzi, A. P. West, D. A. Dougherty, *J. Am. Chem. Soc.* **1996**, *118*, 2307 – 2308; J. C. Ma, D. A. Dougherty, *Chem. Rev.* **1997**, *97*, 1303 – 1324; S. M. Ngola, D. A. Dougherty, *J. Org. Chem.* **1998**, *63*, 4566 – 4567; N. Zacharias, D. A. Dougherty, *Trends Pharmacol. Sci.* **2002**, *23*, 281 – 287; C. A. Hunter, C. M. R. Low, C. Rotger, J. G. Vinter, C. Zonta, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 4873 – 4876.

[9] F. Venema, C. M. Baselier, E. Vandienst, B. H. M. Ruel, M. C. Feiters, J. F. J. Engbersen, D. N. Reinhoudt, R. J. M. Nolte, *Tetrahedron Lett.* **1994**, *35*, 1773 – 1776; P. L. Anelli, M. Asakawa, P. R. Ashton, G. R. Brown, W. Hayes, O. Kocian, S. R. Pastor, J. F. Stoddart, M. S. Tolley, A. J. P. White, D. J. Williams, *J. Chem. Soc. Chem. Commun.* **1995**, 2541 – 2545; M. V. Rekharsky, Y. Inoue, *Chem. Rev.* **1998**, *98*, 1875 – 1917; J. F. Stoddart, D. C. Myles, R. L. Garrell, S. H. Chiu, *Abstr. Pap. Am. Chem. Soc.* **1999**, *218*, 69-CARB; P. R. Ashton, V. Balzani, M. Clemente-Leon, B. Colonna, A. Credi, N. Jayaraman, F. M. Raymo, J. F. Stoddart, M. Venturi, *Chem. Eur. J.* **2002**, *8*, 673 – 684.

[10] F. Diederich, *Cyclophanes*, Royal Society of Chemistry, Cambridge, **1991**; J. E. Forman, R. E. Marsh, W. P. Schaefer, D. A. Dougherty, *Acta Crystallogr. Sect. B-Struct. Commun.* **1993**, *49*, 892 – 896; J. E. Forman, R. E. Barrans, D. A. Dougherty, *J. Am. Chem. Soc.* **1995**, *117*, 9213 – 9228; S. M. Ngola, D. A. Dougherty, *J. Org. Chem.* **1996**, *61*, 4355 – 4360; P. Mattei, F. Diederich, *Helv. Chim. Acta* **1997**, *80*, 1555 – 1588; M. Miyake, C. S. Wilcox, *Heterocycles* **2002**, *57*, 515 – 522.

[11] H. J. Choi, D. J. Cram, C. B. Knobler, E. F. Maverick, *Pure Appl. Chem.* **1993**, *65*, 539 – 543; D. J. Cram, *Container Molelcules and their Guests*, Royal Society of Chemistry, Cambridge, **1994**; J. Y. Yoon, D. J. Cram, *Chem. Commun.* **1997**, 497 – 498; J. F. Stoddart, S. Ro, S. J. Rowan, D. J. Cram, *Abstr. Pap. Am. Chem. Soc.* **1999**, *218*, 112-ORGN; S. Ro, S. J. Rowan, A. R. Pease, D. J. Cram, J. F. Stoddart, *Org. Lett.* **2000**, *2*, 2411 – 2414.

[12] A. Collet, J. P. Dutasta, B. Lozach, J. Canceill, *Top. Curr. Chem.* **1993**, *165*, 103 – 129; M. Miura, S. Yuzawa, M. Takeda, Y. Habata, T. Tanase,

S. Akabori, *Supramol. Chem.* **1996**, *8*, 53–66; P. D. Kirchhoff, J. P. Dutasta, A. Collet, J. A. McCammon, *J. Am. Chem. Soc.* **1999**, *121*, 381–390; Z. L. Zhong, A. Ikeda, S. Shinkai, S. Sakamoto, K. Yamaguchi, *Org. Lett.* **2001**, *3*, 1085–1087.

[13] C. Valdes, U. P. Spitz, L. M. Toledo, S. W. Kubik, J. Rebek, *J. Am. Chem. Soc.* **1995**, *117*, 12733–12745; C. A. Schalley, R. K. Castellano, M. S. Brody, D. M. Rudkevich, G. Siuzdak, J. Rebek, *J. Am. Chem. Soc.* **1999**, *121*, 4568–4579; J. Rebek, *Chem. Commun.* **2000**, 637–643; F. Hof, S. L. Craig, C. Nuckolls, J. Rebek, *Angew. Chem.* **2002**, *114*, 1556–1578; *Angew. Chem. Int. Ed.* **2002**, *41*, 1488–1508; P. Amrhein, A. Shivanyuk, D. W. Johnson, J. Rebek, *J. Am. Chem. Soc.* **2002**, *124*, 10349–10358; J. L. Atwood, A. Szumna, *J. Am. Chem. Soc.* **2002**, *124*, 10646–10647.

[14] F. Vögtle, *Supramolekulare Chemie, 2nd ed.*, Teubner, Stuttgart, **1992**.

[15] F.-G. Klärner, J. Benkhoff, R. Boese, U. Burkert, M. Kamieth, U. Naatz, *Angew. Chem.* **1996**, *108*, 1195–1198; *Angew. Chem. Int. Ed.* **1996**, *35*, 1130–1133; M. Kamieth, F.-G. Klärner, *J. Prakt. Chem.* **1999**, *341*, 245–251; M. Kamieth, U. Burkert, P. S. Corbin, S. J. Dell, S. C. Zimmerman, F.-G. Klärner, *Eur. J. Org. Chem.* **1999**, 2741–2749; F.-G. Klärner, U. Burkert, M. Kamieth, R. Boese, *J. Phys. Org. Chem.* **2000**, *13*, 604–611; R. Ruloff, U. P. Seelbach, A. E. Merbach, F.-G. Klärner, *J. Phys. Org. Chem.* **2002**, *15*, 189–196.

[16] F.-G. Klärner, U. Burkert, M. Kamieth, R. Boese, J. Benet-Buchholz, *Chem. Eur. J.* **1999**, *5*, 1700–1707.

[17] S. P. Brown, T. Schaller, U. P. Seelbach, F. Koziol, C. Ochsenfeld, F.-G. Klärner, H. W. Spiess, *Angew. Chem.* **2001**, *113*, 740–743; *Angew. Chem. Int. Ed.* **2001**, *40*, 717–720.

[18] C.-W. Chen, H. W. Whitlock, *J. Am. Chem. Soc.* **1978**, *100*, 4921–4922; S. C. Zimmerman, C. M. van Zyl, G. S. Hamilton, *J. Am. Chem. Soc.* **1989**, *111*, 1373–1381; S. C. Zimmerman, *Top. Curr. Chem.* **1993**, *165*, 71–102.

[19] M. Kamieth, F.-G. Klärner, F. Diederich, *Angew. Chem.* **1998**, *110*, 3497–3500; *Angew. Chem. Int. Ed.* **1998**, *37*, 3303–3306.

[20] F.-G. Klärner, J. Panitzky, D. Preda, L. T. Scott, *J. Mol. Model.* **2000**, *6*, 318–327.

[21] F.-G. Klärner, J. Panitzky, D. Blaser, R. Boese, *Tetrahedron* **2001**, *57*, 3673–3687.

[22] C. Jasper, T. Schrader, J. Panitzky, F.-G. Klärner, Angew. Chem. **2002**, *114*, 1411–1415; Angew. Chem. Int. Ed. **2002**, *41*, 1355–1358.

[23] F.-G. Klärner, M. Lange, unpublished results.

[24] F.-G. Klärner, B. Kahlert, unpublished results.

[25] The synthesis of **3** was preliminarily published in ref. [15a].

[26] J. Benkhoff, R. Boese, F.-G. Klärner, *Liebigs Ann. Recl.* **1997**, 501–516.

[27] M. P. Cava, D. R. Napier, *J. Am. Chem. Soc.* **1957**, *79*, 1701; M. P. Cava, R. L. Shirley, *J. Am. Chem. Soc.* **1960**, *82*, 654.

[28] M. N. Paddon-Row, H. K. Patney, K. Harish, *Synthesis* **1986**, 328–330.

[29] Compound **13** was prepared by Diels–Alder reaction of 1,3-cyclopentadiene with 1,4-dichloro-2-butene: M. A. P. Bowe, R. G. J. Miller, J. B. Rose, D. G. M. Wood, *J. Org. Chem.* **1960**, 25, 1541–1547. 1,4-dichloro-2-butene was obtained by the reaction of 2-butene-1,4-diol with $SOCl_2$: L. Brandsma, *Preparative Acetylenic Chemistry*, 1st ed., Elsevier, Amsterdam, **1971**; R. Gleiter, R. Merger, B. Nuber, *J. Am. Chem. Soc.* **1992**, *114*, 8921–8927.

[30] P. Schiess, S. Rutschmann, V. Toan, *Tetrahedron Lett.* **1982**, *23*, 3665–3668.

[31] J. Luo, H. Hart, *J. Org. Chem.* **1987**, *52*, 4833–4836; J. L. Segura, N. Martin, *Chem. Rev.* **1999**, *99*, 3199–3246.

[32] The structure of the by-product **21** (not separated and isolated) was derived from the ^{1}H NMR spectrum of the mixture of products after the DDQ dehydrogenation. The spectrum shows, in addition to the signals assigned to **4**, three signals at $\delta = 4.0$, 4.1, and 4.3 ppm as expected for the chemically nonequivalent bridgehead protons of **22**. There is no evidence for the formation of the further possible all-*anti* bisadduct from the ^{1}H NMR spectrum of the mixture of products after DDQ dehydrogenation. This product is expected to show two signals for the bridgehead protons according to its symmetry.

[33] H. Günther, *NMR-Spektroskopie*, Thieme, Stuttgart, **1992**.

[34] A nonlinear regression analysis of Equation (3) (see Experimental Section) was performed by the use of the program TableCurve 4.0, SPSS Science analogous to the computer program HOSTEST by C. S. Wilcox, N. M. Glagovich, University of Pittsburg and the program Associate V1.6, B. Peterson, Ph. D. Dissertation, University of California at Los Angeles, **1994**.

[35] We thank one of the reviewers to focus our attention on the complex stoichiometries and suggesting the Job-plot analysis.

[36] Titration experiments were performed on a TAM 2277 microcalorimeter (Thermometric, Järfälla, Sweden) using the ampoule unit 2277-201. The addition of the solution during the titration experiment was managed with syringe-pump 6120-031, Lund, Sweden.

[37] The ^{1}H NMR spectrum of the 2:1 mixture of **4** and **32** also shows temperature-dependent behavior, comparable to that of a 2:1 mixture of **2** and **32**. This will be reported separately, with respect to the kinetic stability of these host–guest complexes and the mobility of the guest molecules inside host cavity.

[38] SPARTAN 02, Wavefunction, Inc., 18401 Von Karman, Suite 370, Irvine, California 92715.

[39] C. Ochsenfeld, F. Koziol, S. P. Brown, T. Schaller, U. P. Seelbach, F.-G. Klärner, *Solid State Nucl. Mag. Reson.* **2002**, *22*, 128–153.

[40] C. Ochsenfeld et al., unpublished results.

[41] Compound **8** can be obtained from indene in four steps according to D. N. Butler, R. A. Snow, *Can. J. Chem.* **1975**, *53*, 256–262 (simplified by M. Kamieth, Diplomarbeit, Universität Essen, **1995**).

Received: March 4, 2003 [F4919]

