Molecular Tweezers and Clips as Synthetic Receptors. Molecular Recognition and Dynamics in Receptor−Substrate Complexes

FRANK-GERRIT KLÄRNER* AND BJÖRN KAHLERT

Institut für Organische Chemie, Universität Duisburg-Essen, 45117 Essen, Germany

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ABSTRACT

The molecular tweezers (**1**, **2**) and clips (**3**−**7**) containing naphthalene and benzene spacer units can be synthesized via repetitive Diels−Alder reactions by the use of a molecular "Lego" set consisting of bisdienophiles (**8**, **9**, **14**) and dienes (**10**, **13**). The new receptors selectively bind electron-deficient neutral and cationic substrates in solution. Only the benzene-spaced tweezers form complexes with aliphatic substrates, whereas the other receptors bind aromatic substrates preferentially. HPLC studies with **1** and **2** chemically bonded to stationary phases give similar results for the heterogeneous systems. The formation of stable complexes between the water-soluble clip **5g** and *N*-alkylpyridinium cations, such as *N*-methylnicotinamide and NAD^+, in aqueous solution illustrates the importance of the hydrophobic effect for arene−arene interactions. The dynamics of the complex formation and substrate mobility were investigated by the use of temperature-dependent liquid- and solid-state NMR spectroscopy. The electrostatic potential surface (EPS) of **1**−**7** is calculated to be surprisingly negative on the concave side of each molecule and, hence, complementary to the EPS of the electron-deficient substrates, suggesting that the attractive receptor−substrate interaction is here of predominantly electrostatic nature.

Introduction

The processes of molecular recognition and self-assembly/self-organization are of fundamental importance for the formations of higher organized chemical systems that result from the association of two or more chemical species.[1] These processes depend on weak but specific, mostly noncovalent intermolecular interactions, such as hydrogen bonding,[2] ion pairing,[3] and arene−arene interactions,[4−7] in addition to the less specific van der Waals or dispersion forces. Furthermore, coordinative metal−ligand bonds are today frequently used for the programmed synthesis of supermolecules.[8] The solvent often plays an active role in these processes by solvating or desolvating the interacting molecules during the receptor−substrate association. In particular, the hydrophobic effect in aqueous media can be very strong and can determine the stability of the associates to a substantial extent.[4]

These noncovalent interactions play a key role in many biological processes, such as protein folding, the bonding and catalytic transformation of substrates by enzymes, the formation of membranes and the transportation of neutral and ionic species through membranes, and the expression and transfer of genetic information. *Multiple weak bonds are necessary to form supermolecules which are, on one hand, sufficiently stable under normal conditions (e.g., room temperature in aqueous solution) and, on the other hand, sufficiently flexible to undergo conformational changes and partial or complete dissociation without changing these conditions dramatically.* Today, the intermolecular interactions and particularly the interplay between substrate and receptor via multiple noncovalent bonds are experimentally as well as theoretically studied by means of relatively simple synthetic receptors which can act as models for the far more complicated biological systems. Besides the well-preorganized macrocycles, such as cyclodextrins,[9] cyclophanes,[10−12] carcerands,[13] cryptophanes,[14] cucurbit[*n*]urils (CB[*n*]),[15] and supramolecular capsules[16] (formed by self-assembly of suitable molecular building blocks), noncyclic compounds with cavities of flexible size, which are frequently termed as molecular tweezers[17] and clips,[18] proved to be effective as synthetic receptors. In this Account we focus on multiple noncovalent interactions of arene units in the receptor with neutral or ionic aromatic substrates ($\pi-\pi$, CH$-\pi$, and cation$-\pi$ interactions). Representative examples of synthetic receptors binding aromatic substrates preferentially are shown in Scheme 1. Classical examples of aromatic interactions are the base stacking in DNA and the protein folding caused by phenylalanine and other aromatic amino acid side-chain interactions.[19] The preference of the edge-to-face over the face-to-face orientation of two benzene rings, as found in the crystal structure of benzene[20] or in the protein structures mentioned above, can be explained with a simple electrostatic model for benzene consisting of a positively charged σ framework sandwiched between two clouds of π electron density. Quantum mechanical calculations predict a displaced face-to-face orientation slightly more stable than the edge-to-face configuration.[4−6] Besides gas-phase investigations, there are several experimental studies in solution to quantify the noncovalent arene−arene interactions, for example, by measuring the rotational barrier in 1,8-diarylnaphthalene derivatives,[21] the equilibrium between a folded and open conformation of the so-called torsional balance,[7] and a chemical double-

Frank-Gerrit Klärner studied chemistry at the University of Köln (Cologne) and received his Ph.D. in 1968 from the University of Köln. In 1974, he finished his "Habilitation" at the Ruhr-University of Bochum, was associate professor in Bochum from 1980 to 1992, and was visiting professor at the University of Wisconsin, Madison, in 1983. Since 1992, he is full professor at the University of Essen and chairs the DFG center of supramolecular research at the Universities of Essen and Bochum ("Sonderforschungsbereich, SFB 452") since 1998. His research interests are in the field of supramolecular chemistry (molecular recognition, development of synthetic receptors for bioactive chemical compounds) and high-pressure chemistry (up to 14 kbar).

Björn Kahlert studied chemistry and received his diploma degree ("Diplomchemiker") from the University of Essen in 2001, and is currently working as a Ph.D. student in Klärner's research group in Essen. He is interested in the functionalization of synthetic receptors and in computational modeling of host−guest complexes.

* To whom correspondence should be addressed. E-mail: frank.klaerner@uni-essen.de.

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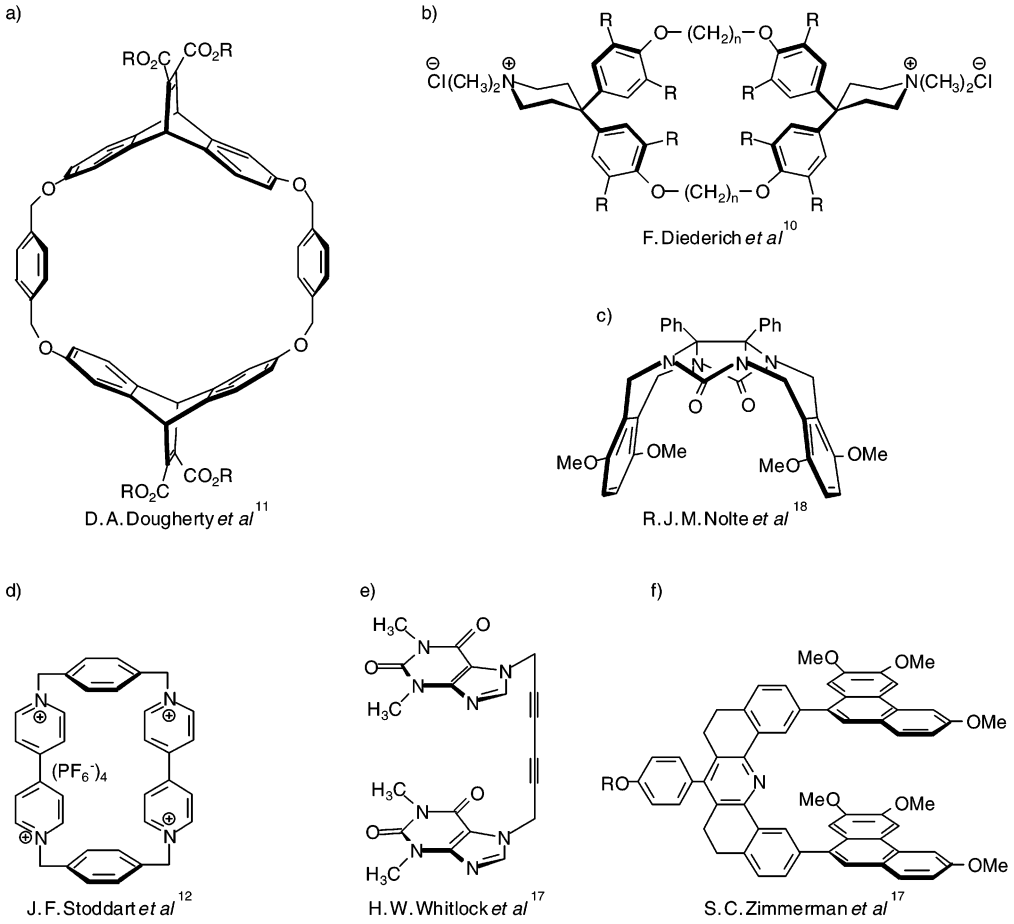
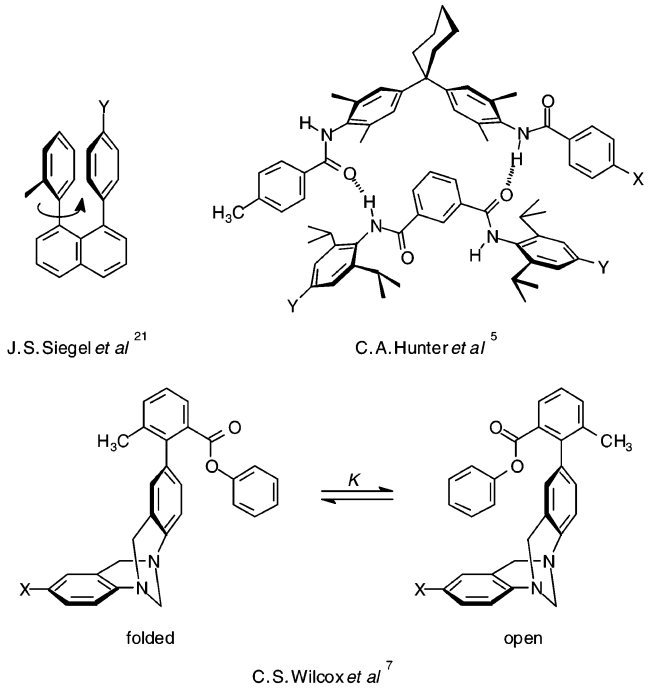
Scheme 1. Examples of Macrocycles, Molecular Tweezers, and Clips as Receptors for Aromatic Substrates



mutant cycle by replacing one of the terminal substituted benzene rings after the other with alkyl groups in the bimolecular complex[5] shown in Scheme 2 and determining the Gibbs enthalpy of association for each complex. More detailed information on the subject of aromatic interactions can be found in two reviews which recently appeared.[4,5]

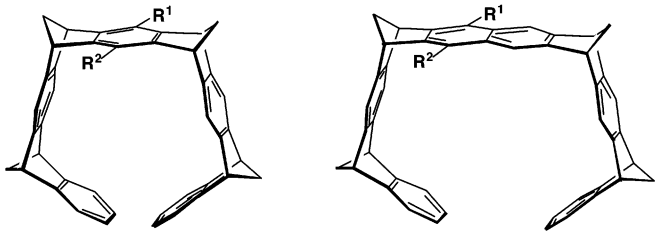
In the following we discuss the syntheses and supramolecular functions of the molecular tweezers (**1**, **2**) and clips (**3**−**7**) (Scheme 3) which have not been surveyed to date. These molecules are well preorganized because of their belt-type structures. *But bond angle distortions require little energy and, therefore, should induce a certain flexibility in these systems, allowing the receptor "arms" to be expanded and compressed during the substrate complexation in a way comparable to the working principle of mechanical tweezers.* Thus, a fit of the receptor geometry to the substrate topography to a certain extent, induced by the complex formation, can be expected. The size and shape of the receptor cavities can be systematically varied by varying the number and size of the spacer units. Finally, the parent compounds **1a**−**7a** are simple hydrocarbons containing only nonconjugated benzene and/or naphthalene rings arranged in a belt-like concave−convex topography, so that an aromatic substrate can be bound via multiple $\pi-\pi$ and CH$-\pi$ interactions. Here the question can be addressed of whether the magnitude of the complex stabilization is dependent on the orientation

Scheme 2. Various Dynamic Equilibrations Quantify the Edge-to-Face Arene−Arene Interaction

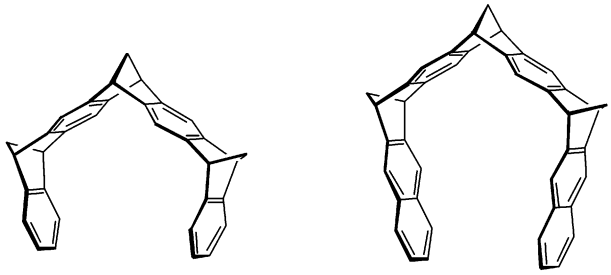


of the multiple arene−arene interactions, comparable to the multiple hydrogen bonding, where, for example, the

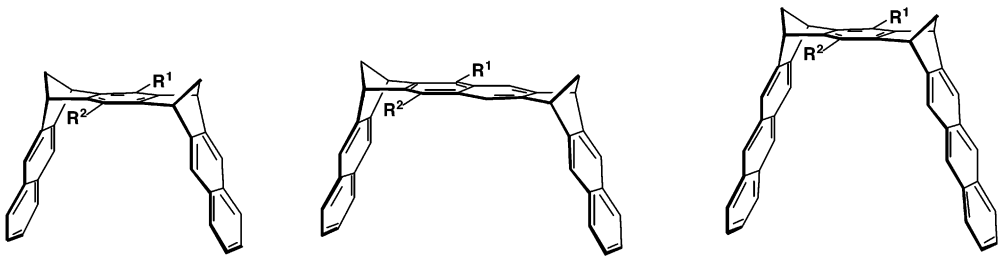
Scheme 3. Structures of the Tetra-, Tri-, and Dimethylene-Bridged Tweezers and Clips Synthesized to Date



1 **2**



3 **4**



5 **6** **7**

R^1	H	OAc	OH	OMe	OCH_2CO_2Et	$OCH_2CO_2^-$	$OP(CH_3)O_2^-\ ^+N(n\text{-}Bu)_4$
R^2	H	OAc	OH	OMe	OCH_2CO_2Et	$OCH_2CO_2^-$	$OP(CH_3)O_2^-\ ^+N(n\text{-}Bu)_4$
	a	**b**	**c**	**d**	**e**	**f**	**g**

R^1	OAc	OAc	OH	OMe
R^2	OH	OCH_2CO_2Et	$OCH_2CO_2^-$	$O(CH_2)_4\text{-}CH{=}CH_2$
	h	**i**	**j**	**k**

Scheme 4. Synthesis of Tetra- and Trimethylene-Bridged Tweezers and Clips 1−4

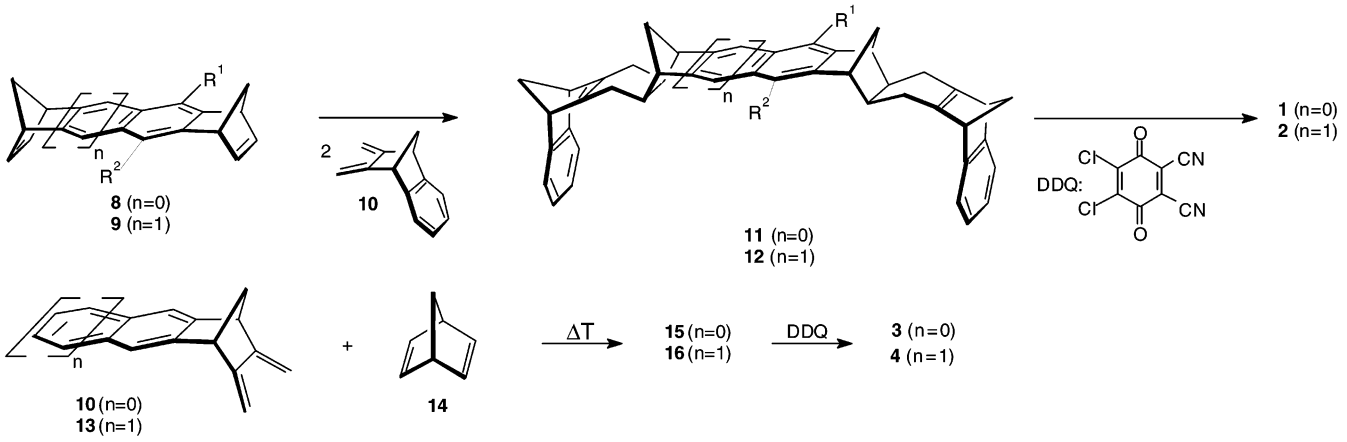


Table 1. Maximum Complexation-Induced ^{1}H NMR Shifts of the Substrate Protons, $\Delta\delta_{max} = \delta_0 - \delta_{complex}$, Association Constants, K_a (M^{-1}), and Gibbs Enthalpy, ΔG (kcal/mol), for the Formation of Host−Guest Complexes in $CDCl_3$ at 21 °C (1a, 2a) and 25 °C (4), Respectively

	receptor **1a**			receptor **2a**			receptor **4**		
substrate	K_a	ΔG	$\Delta\delta_{max}$	K_a	ΔG	$\Delta\delta_{max}$	K_a	ΔG	$\Delta\delta_{max}$
				(a) Neutral					
p-DCNB **21**	10	−1.3	3.5	110	−2.8	4.3	44	−2.2	2.8
m-DCNB **22**				85	−2.6	5.3 (H[a])	40	−2.2	1.5 (H[a])
o-DCNB **23**				40	−2.1	5.2 (H[a])	11	−1.4	3.1 (H[a])
TCNB **24**				$>10^5$	<−6.7	5.9	$>10^5$	<−6.7	4.7
TA **25**				35	−2.1	1.6			
p-DNB **26**	17	−1.7	3.5	45	−2.2	5.5	63	−2.4	3.0
FDNB **27**							49	−2.3	4.3 (H[a])
TNF **28**							130	−2.9	4.6 (H[a])
TFB **29**				26	−1.6	1.2			
Pyr **30**				8	−1.2	1.3			
p-BQ **31**				20	−1.8	2.8			
TCNQ **32**	1100	−4.8	2.9	$>10^5$	<−6.7	3.6	2600	−4.6	3.3
CH_3CN	15	−1.6	5.3						
$CH_2(CN)_2$	36	−2.1	4.5						
				(b) Cations					
Kosower salt **33**				1100	4.1	4.1 (H[a])	122	−2.8	3.7 (H[a])
MePyrI **34**	3500	−4.8		35000	−6.1				
MeVio **35a**	56[a]	−2.4	1.5 (H[a])						
DeVio **35b**	130[b]	−2.9	1.6 (H[a])				990	−4.0	0.7 (H[a])
Bz*Vio **35c**				4400[a,d]	<−5.0	4.6			
$TrpBF_4$ **36**	25[b]	−1.9	2.5	2600[c,d]	−4.7	2.9			
n-$Bu_2NH_2BF_4$ **37**	30	−2.0	3.2 (α-H)						

[a] In $CDCl_3$/acetone-d_6 (1:2). [b] In $CDCl_3$/acetone-d_6 (1:1). [c] In acetone. [d] Determined with **2b** as receptor.

Table 2. $\Delta\delta_{max}$, K_a (M^{-1}), and ΔG (kcal mol^{-1}) for the Formation of Host−Guest Complexes in $CDCl_3$ at 25 °C

	receptor **5c**			receptor **7c**		
substrate	K_a	ΔG	$\Delta\delta_{max}$	K_a	ΔG	$\Delta\delta_{max}$
TCNB **24**	2180	−4.6	3.6	4870	−5.0	4.8
p-DNB **26**	16	−1.6	1.4			
FDNB **27**				246	−3.3	0.5 (H[a])
TNF **28**	45	−2.3	1.2 (H[a])	4930	−5.0	1.5 (H[e])
TCNQ **32**	137	−2.9	2.6	676	−3.9	3.3
Kosower salt **33**	1080	−4.1	2.4 (H[a])	2350	−4.6	3.0 (H[a])
DeVio **35b**[a]				73	−2.5	1.3 (H[a])

[a] Measured in $CDCl_3$/acetone-d_6 1:1.

Table 3. Enthalpies, ΔH (kcal mol^{-1}), Entropies, ΔS (cal mol^{-1} K^{-1}), and Volumes, ΔV (cm^3 mol^{-1}), of Association at 25 °C in $CDCl_3$[27]

	receptor **2a**			receptor **2b**		
substrate	ΔH	ΔS	ΔV	ΔH	ΔS	ΔV
p-DCNB **21**	−2.6	+0.5	+1.5	−1.9	+7.6	
p-DCNB **21**[a]	−3.8	−3.1	−1.1	−3.8	−0.2	−1.1
TA **25**	−6.0	−14.1	+0.6	−2.2	−2.4	
p-BQ **31**	−6.5	−15.3	−3.0	−2.6	−3.8	

[a] In benzene-d_6.

interaction between donor−donor (D−D) and acceptor−acceptor (A−A) is more stable than that between D−A and A−D.[22]

Convergent Syntheses of Molecular Tweezers and Clips

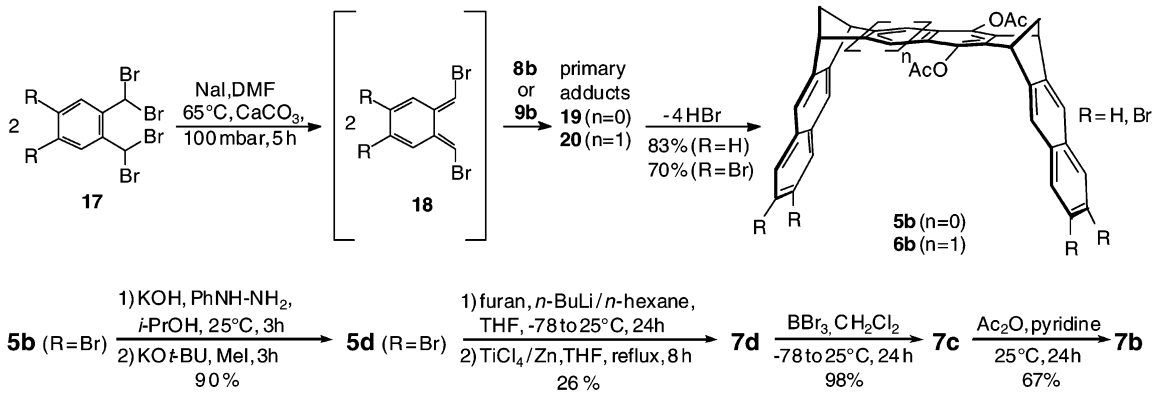
The tweezer and clip molecules **1**−**7** can be synthesized by the use of a molecular "Lego" set consisting of bisdienophiles such as **8**, **9**, and **14** and dienes such as **10** and **13**. The key steps in the synthesis of the tetra- and trimethylene-bridged systems **1**−**4** are repetitive Diels−Alder reactions, proceeding with a high degree of stereoselectivity on the exo face of the bisdienophiles **8**, **9**, and **14** and on the endo face of the dienes **10** and **13**, leading to the bisadducts **11**, **12** and **15**, **16**, respectively, with the methylene bridges in each adduct syn to one another (Scheme 4). Oxidative dehydrogenation of the cyclohexene moieties in **11**, **12** and **15**, **16** by the use 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) produces **1**−**4** in reasonable overall yields (11−60%).[23,24]

The dimethylene-bridged clips **5b** and **6b** can be synthesized in one-pot reactions analogously starting from **8b** or **9b** as one building block and tetrabromoxylene **17** (R = H) or hexabromoxylene **18** (R = Br) as a precursor of the other one. The synthesis of **7b**−**d** could be accomplished by a sequence of reactions starting from the clip **5b** (R = Br) (Scheme 5). The derivatives **a**−**k** can be prepared by the transformation of the acetate groups into the other functional groups by standard methods.[24−26]

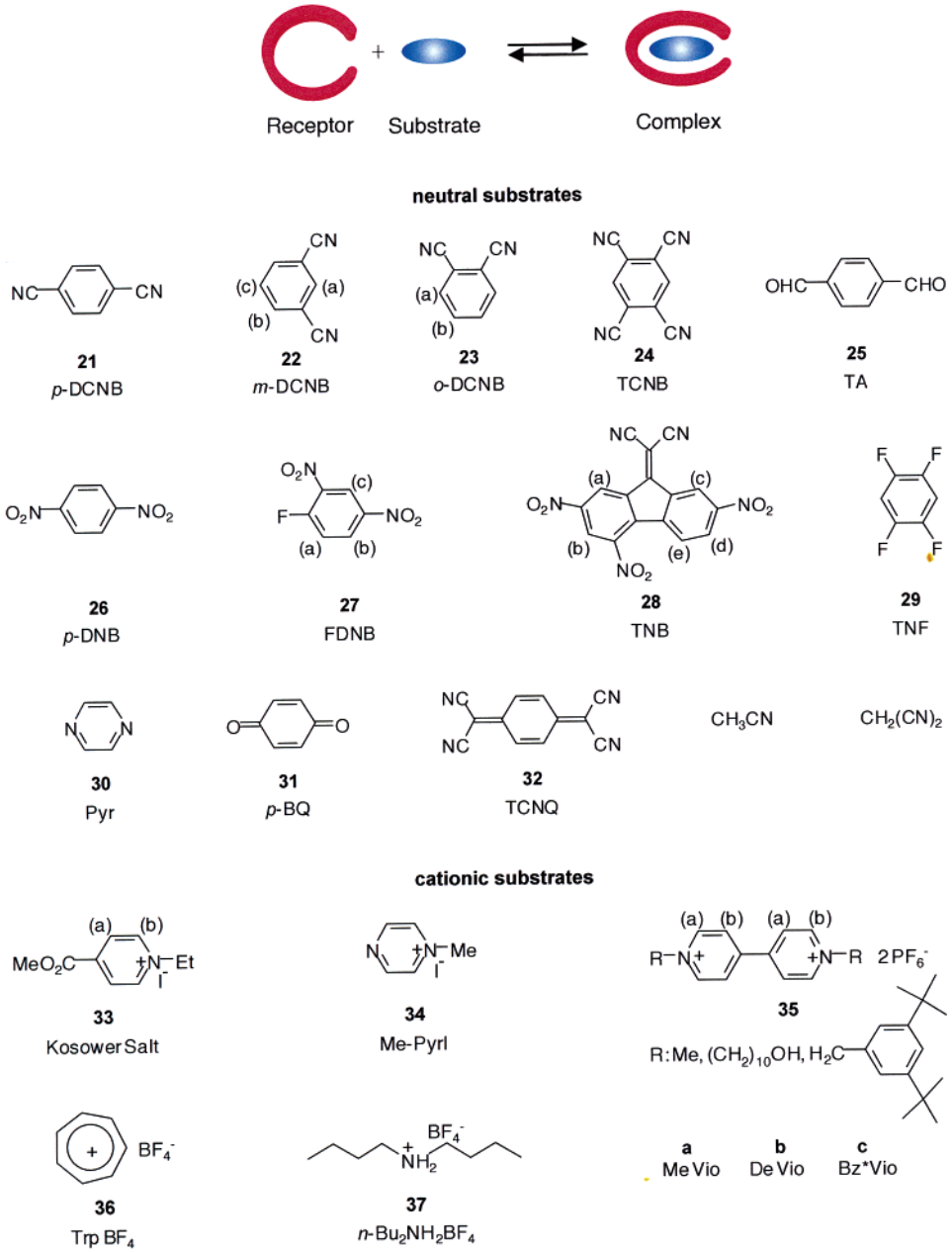
Thermodynamic Parameter of the Complex Formation

The magnetic anisotropy of the receptor arene units makes ^{1}H NMR spectroscopy a very sensitive probe for uncovering the complexation of substrate molecules inside the cavities of **1**−**7**. The complex formation can be easily detected by pronounced upfield shifts of the substrate signals in the ^{1}H NMR spectrum of a mixture consisting of one of the receptor molecules **1**−**7** and one of the substrate molecules shown in Scheme 6. The maximum complexation-induced NMR shifts, $\Delta\delta_{max}$, of the substrate protons, the association constants, K_a, and, hence, the Gibbs enthalpies of association, ΔG, were determined by ^{1}H NMR titration experiments. The molecular tweezers and clips **1**−**7** bind a variety of electron-deficient neutral and cationic substrates inside their cavities. Comparison of the naphthalene-spaced tweezer **2a** with its smaller benzene-spaced analogue **1a** (Table 1) demonstrates that **2a** is a better receptor for aromatic substrates than **1a**,

Scheme 5. Synthesis of the Dimethylene-Bridged Clips 5–7



Scheme 6. Survey of the Substrates Forming Complexes with 1–7 as Receptors[a]



[a] The complex formation may induce a conformational change in the receptor.

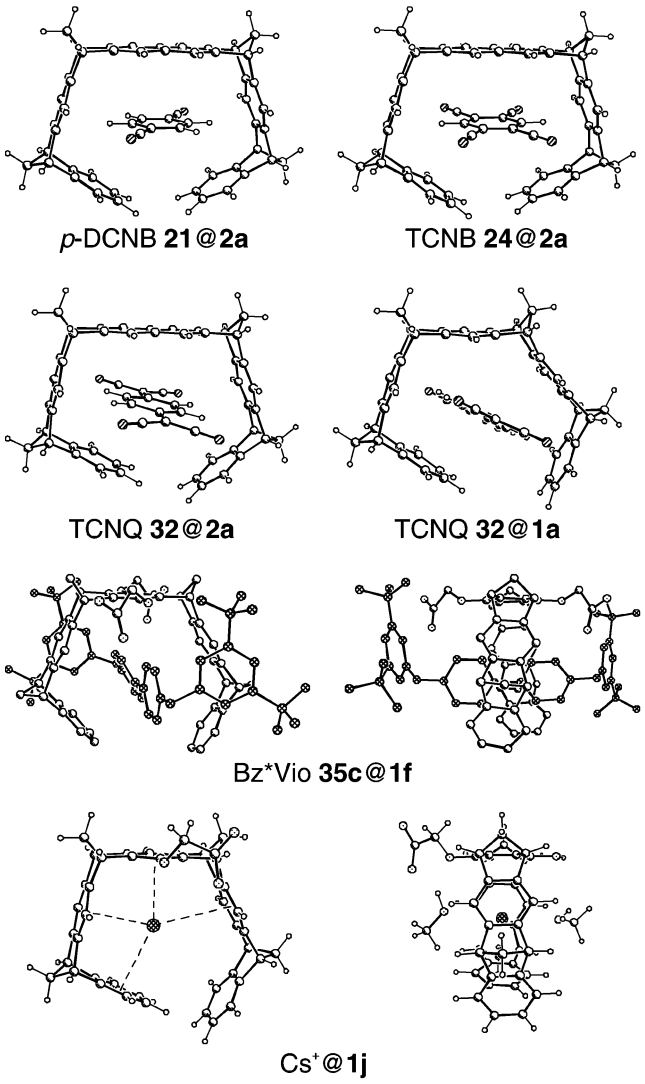


FIGURE 1. Single-crystal structure analyses of the complexes between molecular tweezers and various arenes and Cs^+ as substrates[24,26] (depository numbers: CSD 408726 (**21@2a**), 408724 (**32@2a**), and 408725 (**32@1a**).

whereas aliphatic substrates such as acetonitrile or malononitrile are only complexed inside the smaller cavity of **1a**. The clip **4** is, accordingly, a better receptor for aromatic substrates than **1a**, but a poorer receptor than **2a** for substrates such as **21**−**24**, **32**, and **33**, bearing "small" substituents such as the linear sp-hybridized cyano group or nonbranched alkyl groups. With sterically more demanding substrates, such as **26**−**28**, **4** forms stabler complexes than **2a**. Similar receptor properties are observed for the dimethylene-bridged clips **5** and **7** (Table 2). Because of the reduced number of methylene bridges, from 4 to 3 to 2, the topography of the clip molecules **4**−**7** is more open than that of the tweezers **1** and **2**, allowing sterically larger substrates to be included into the cavities of these clip molecules. The finding that the anthracene clip **7c** forms stabler complexes than the naphthalene clip **5c** can be explained by the larger van der Waals contact surface of the anthracene sidewalls.

The thermodynamic parameters of the complex formation—the enthalpy, ΔH, entropy, ΔS, and volume of association, ΔV—were determined from the temperature or pressure dependence of the association constants, K_a, by the use of variable-temperature and variable-pressure ^{1}H NMR analyses.[24,27] Illustrative data (Table 3) indicate that the complex formation is largely the result of an enthalpic receptor−substrate interaction ($\Delta H < 0$). The entropies of association vary in a relatively broad range ($\Delta S = -15.3$ to $+7.6$ cal mol^{-1} K^{-1}). The volumes of association show, however, only a small variation around the zero value ($\Delta V = -3.0$ to $+1.5$ cm^{3}mol^{-1}). The decrease in volume resulting from the complexation of the substrate is obviously more or less compensated by the increase in volume caused by the desolvation of substrate and receptor (release of solvent molecules) during the complexation. Association and desolvation are expected to give a correspondingly negative or positive contribution to the entropy. But there is no correlation between the entropies and volumes of association (Table 3). Consequently, the large differences observed for the entropies of association cannot only be the result of these contributions. To explain this contradiction, the mobility (the conformational freedom) of the substrate inside the receptor cavity (vide infra) has been assumed to provide a significant contribution to ΔS while having only a small influence on ΔV.

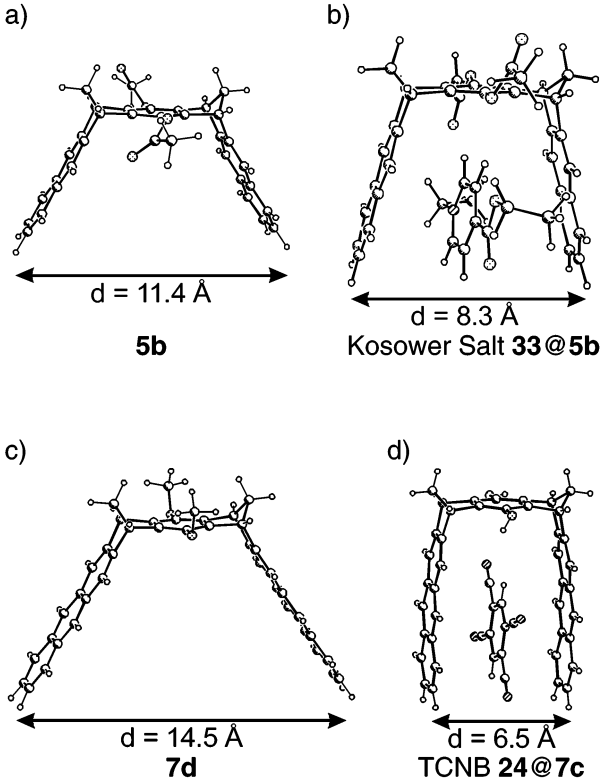


FIGURE 2. Single-crystal structure analyses of (a) the clip **5b**, (b) the complex **33**@**5b**,[25] (c) the clip **7d**, and (d) the complex TCNB **24**@**7c**[28] (d = terminal CC distance).

Complex Structures and Dynamics

The structures of several complexes could be determined by single-crystal structure analyses. According to the

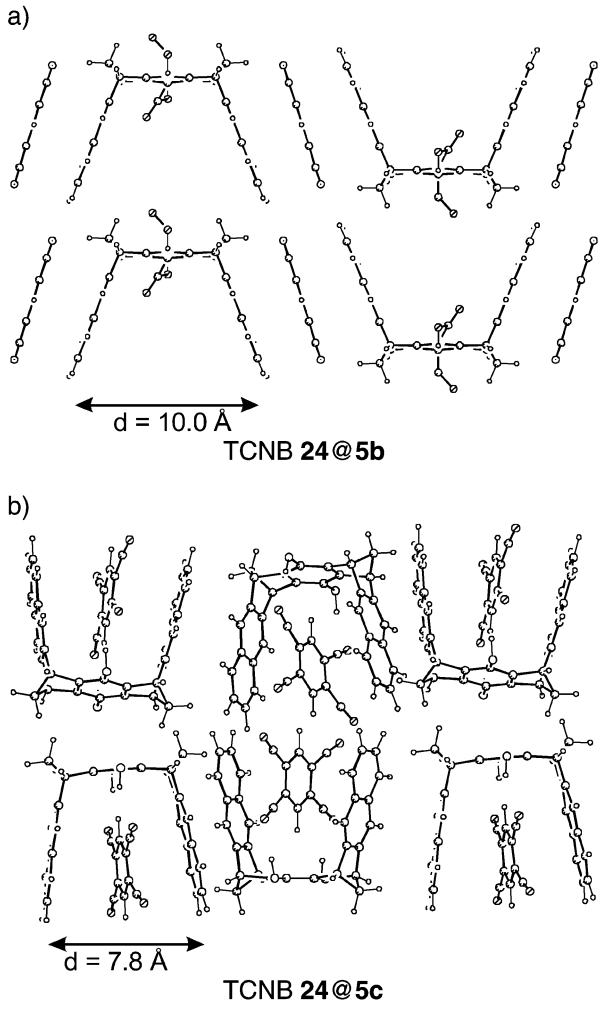


FIGURE 3. Single-crystal structure analyses of (a) cocrystals of TCNB **24** and empty **5b** and (b) the complex TCNB **24**@**5c**[25] (*d* = terminal CC distance).

structures shown in Figures 1[24] and 2,[26] the naphthalene-spaced tweezer **2a** has an almost ideal topography for the complexation of benzene derivatives, while the complexation of these substrates by the benzene-spaced tweezer **1a** requires a substantial distortion of the receptor geometry.

This distortion certainly explains why the complexes of aromatic or quinoid substrates with the benzene-spaced receptor **1** are less stable than the corresponding complexes of the naphthalene-spaced receptor **2**. The benzene-spaced tweezers **1j**,**f** surprisingly form complexes with the cesium cation Cs^+. The formation of $(Cs^+)_2$@**1f** can be detected in its ^1H NMR spectrum in CD_3OD by the downfield shift of the OCH_2COO^- signal ($\Delta\delta = -0.15$). According to the single-crystal structure (Figure 1), the Cs^+ cation interacts with four of the five benzene units inside the cavity of **1j**. No complexation is observed for the corresponding potassium salts. Cs^+ has obviously the optimum size (ionic radius 167 pm), whereas K^+ (133 pm) is too small for these multiple attractive cation−arene interactions, so the stability usually observed for 1:1 alkali metal cation−arene complexes ($Li^+ > Na^+ > K^+ > Cs^+$) is reversed in this case for $K^+ < Cs^+$.

According to the single-crystal structures (Figure 2), the distance between the naphthalene sidewalls in the dimethylene-bridged clip **5b** has to be compressed from 11.4 Å in empty **5b** to 8.3 Å in the complex **33**@**5b**. The increase in steric strain resulting from this compression is certainly one reason the complexes of **5** are usually less stable than those of the tetra- and trimethylene-bridged receptors **2** and **4**.[25] A larger and even more impressive compression of this distance from 14.5 to 6.5 Å is observed for the formation of the TCNB complex of the anthracene clip **7b**.[28]

According to force-field calculations,[29] the expansion and compression of the sidewalls by angle distortion and out-of-plane deformation of the aromatic sidewalls in **5a** and **7a** are low-energy processes. For example, the compressions from 10 (the global minimum) to 8 Å in **5a** and from 12.4 to 6.5 Å in **7a** are calculated to require an energy of about 1.5 and 3.5 kcal/mol, respectively, which is,

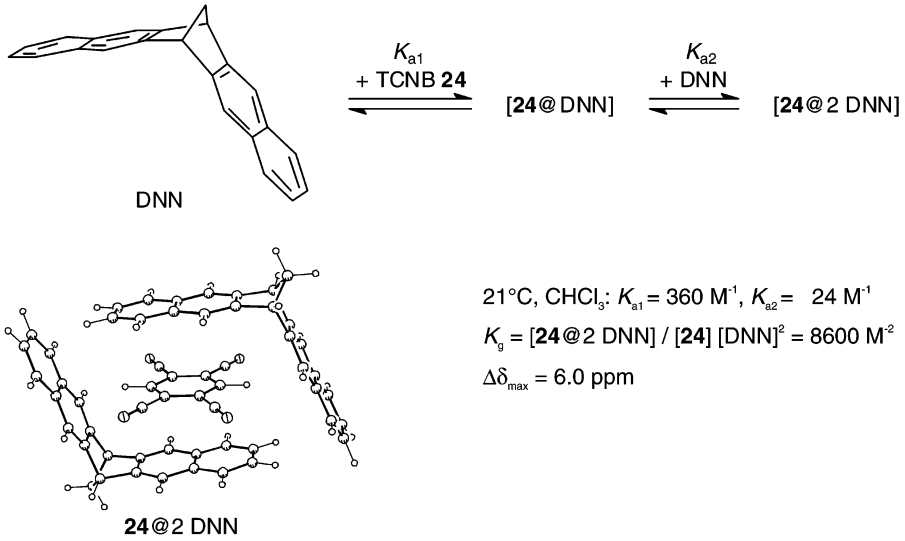
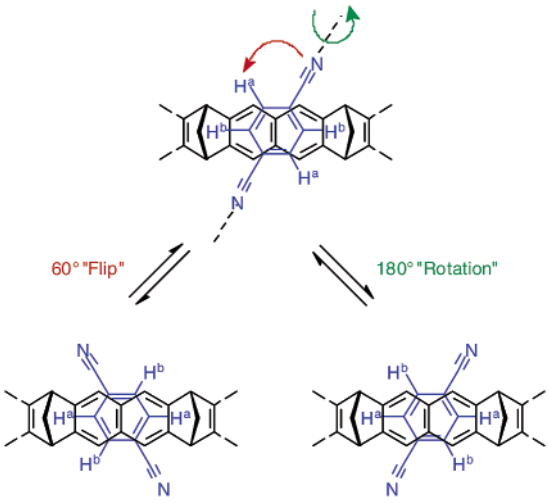


FIGURE 4. Formation and single-crystal structure of the 2:1 complex **24**@2DNN.[25]

^{1}H NMR	$CDCl_3$	solid-state	computed[a]
H^a	3.5 (4.3)	5.6 (2.2)	5.3 (2.7)
H^b	3.5 (4.3)	2.0 (5.8)	1.7 (6.3)

coalescense of the signals of H^a, H^b in the solid-state ^{1}H NMR at 137°C: $\Delta G^{\neq} = 17.2$ kcal/mol.



a) *ab initio* calculation (GIAO-HF/TZP)

FIGURE 5. ^{1}H NMR shifts, δ, and the complexation-induced shifts, $\Delta\delta_{max}$, in parentheses, of the guest protons (H^a, H^b) in **21**@**2a**, and $\Delta G^{\ddagger}$ for the exchange of H^a and H^b in the solid state.[30,31]

apparently, overcompensated by the noncovalent attractive substrate−receptor interactions in the complexes of **5** and **7**. Interesting cases are the structures of the TCNB complexes of the diacetate and hydroquinone clips **5b**,**c**. In $CHCl_3$ solution, **5b** binds TCNB **24** inside the cavity ($\Delta\delta_{max} = 3.44$, $K_a = 140$ M^{-1}, 21 °C), whereas in the cocrystal the TCNB molecule is located between the naphthalene units of two molecules of **5b** outside the receptor cavity, which is empty in this case (Figure 3a).[25] Evidently, in the cocrystal the noncovalent interactions between one TCNB molecule **24** and the naphthalene units of two different clip molecules **5b** are stronger than the "intramolecular" interactions between **24** 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 sidewalls is required for an optimal substrate−receptor interaction. In solution, however, the 2:1 arrangement of **5b** and **24** observed in the cocrystal is certainly disfavored because of the highly negative entropy term expected for a termolecular associate. The hydroquinone clip **5c** forms a substantially more stable complex with **24** (in $CHCl_3$, $\Delta\delta_{max} = 3.57$ $K_a = 2180$ M^{-1}, 21 °C) than the diacetate clip **5b**, most likely because of the additional O−H- - -N hydrogen bonds and the smaller steric demand of the OH group (compared to OAc). In this case, the substrate **24** is bound inside the cavity in both states in the cocrystal as well as in solution.[25] Dinaphthonorbornadiene (DNN, "the monomethylene-bridged receptor") forms a 2:1 complex with TCNB **24** in the crystal and in solution as well (Figure 4).[25] In the crystalline state, the complex shows an optimal arrangement of the TCNB molecule between two DNN molecules,

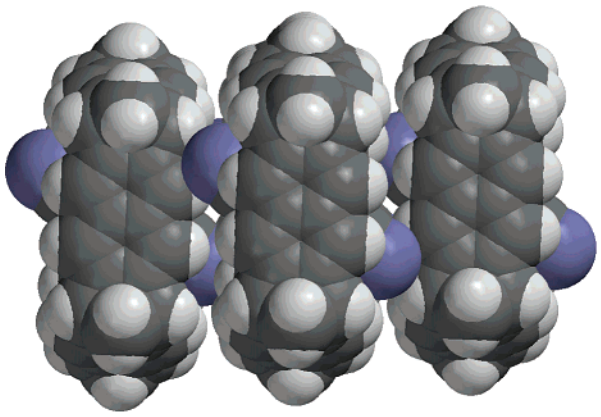


FIGURE 6. Top view on the crystal lattice of the complex *p*-DCNB **21**@**2a**.

without any distortion of the receptor geometry, experiencing attractive CH−π and slipped face-to-face π−π interactions between TCNB and the naphthalene rings of DNN.

Evidently, the gain in energy resulting from this arrangement overcompensates the unfavorable entropy term for the formation of a termolecular associate. Thus, the 2:1 complex is also stable in solution. Besides the discussed single-crystal structures, the complexation-induced ^{1}H NMR shifts, $\Delta\delta_{max}$, of the substrate protons provide important information on the complex structures, as has been recently shown for the complex of *p*-DCNB **21** with the naphthalene tweezer **2a**. In its solid-state ^{1}H NMR spectrum, two signals at $\delta = 5.6$ and 2.0 can be assigned to the substrate protons H^a and H^b (Figure 5).[30] The chemical shifts of H^a and H^b computed by quantum chemical ab initio methods are in good agreement with the solid-state ^{1}H NMR data.[30,31] In the ^{1}H NMR spectrum of *p*-DCNB **21**@**2a** in solution, only one signal at $\delta = 3.5$ is observed for H^a and H^b, even at low temperature (−70 °C), indicating that in solution the exchange of the nonequivalent protons H^a and H^b, resulting from mutual complex dissociations−association and/or rotation of the substrate *p*-DCNB **24** inside the tweezer cavity, is fast with respect to the NMR time scale over a broad range of temperatures (from +21 to −70 °C). In the solid-state ^{1}H NMR spectrum, however, a broadening and finally a coalescence of the separated signal of H^a and H^b can be observed upon heating to 137 °C. Two dynamic processes can be envisaged, which are consistent with the exchange of H^a and H^b, namely either a 180° "rotation" around the long axis of the substrate or a 60° "flip" between the two equivalent sites in the complex (Figure 5). According to quantum chemical and force-field calculations, the 60° "flip" has a very low activation barrier (≤2 kcal/mol) and seems to be clearly favored over the 180° "rotation" (calculated activation barrier ca. 8 kcal/mol) from the energy. These results certainly explain the missing temperature dependence of the solution-state ^{1}H NMR spectrum of *p*-DCNB **21**@**2a**. However, if a larger fragment of the solid-state structure is considered (Figure 6),[24] it becomes clear that the 60° "flip" would move the CN groups of the substrate in the transition state too close to

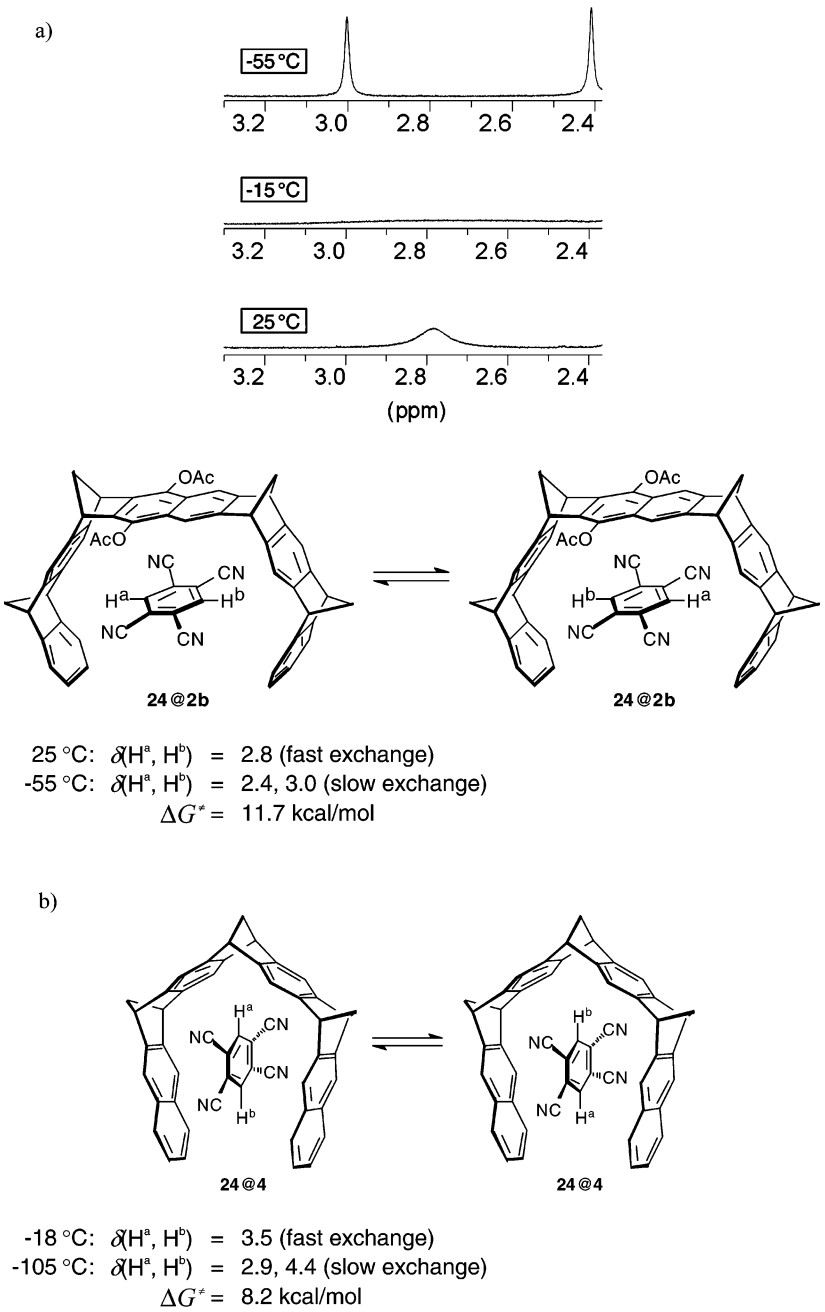


FIGURE 7. Temperature-dependent ^{1}H NMR spectra of (a) **24**@**2b** and (b) **24**@**4** in toluene-d_8.

the atoms of the neighboring complex. That prevents this motion and leads to the conclusion that the exchange of H^a and H^b in the solid state occurs via the 180° "rotation", which does not affect the positions of the CN groups relative to each other. TCNB **24** forms a very stable, bright yellow complex with the naphthalene tweezer **2a** (CT absorption, λ_{max} = 420 nm), showing a complexation-induced ^{1}H NMR shift of the TCNB protons by $\Delta\delta_{max}$ = 5.9 in solution, which is of comparable size to the $\Delta\delta_{max}$ value of H^b in the solid-state ^{1}H NMR spectrum of *p*-DCNB **21**@**2a**.[24]

Evidently, the structure of the TCNB complex in solution closely resembles that in the crystalline state. In the TCNB complexes of the diacetoxy-substituted tweezer **2b** and trimethylene-bridged clip **4**, the TCNB protons are expected to be chemically nonequivalent. In the ^{1}H NMR spectrum of each complex (at 298 or 255 K), only one signal for both protons is observed, which is broadened by lowering the temperature and finally split into two signals (at 218 or 168 K). These exchange processes can be explained by a rotation of the TCNB molecule inside the tweezer or clip cavity. From the line-shape analyses, the Gibbs activation enthalpies were determined to be $\Delta G^{\ddagger}$ = 11.7 and 8.2 kcal/mol, respectively.[32] The activation barriers calculated by force field (MMFF 94)[29] are of the same order of magnitude. These processes can be considered to be the dynamic equilibration of noncovalent conformers (Figures 7and 8). In the ^{1}H NMR spectra of 2:1 mixtures of receptors such as **2a**,**b** and **4** and substrates

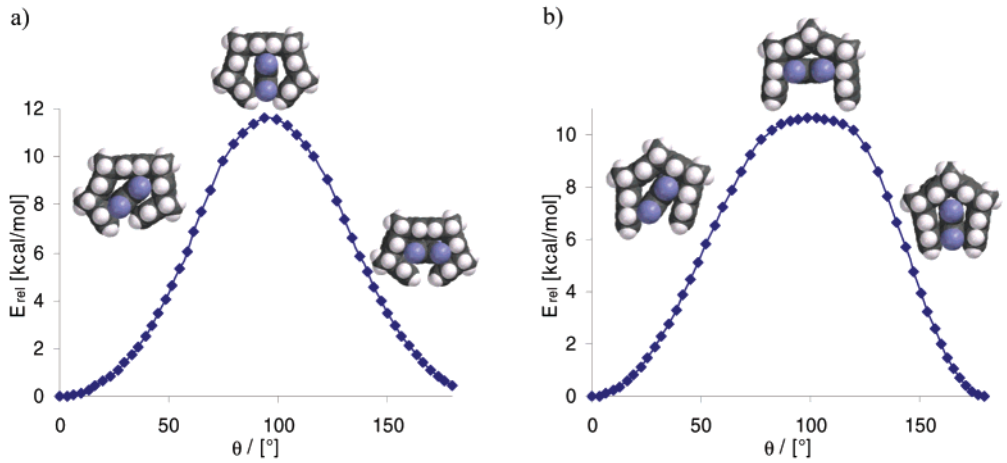
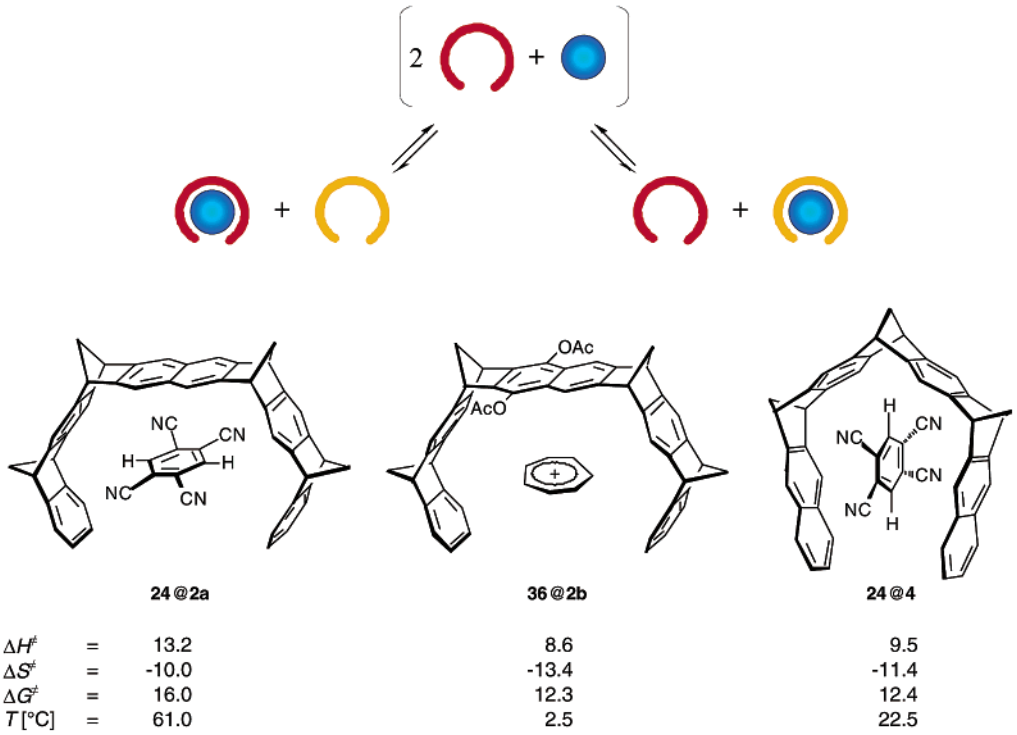


FIGURE 8. Activation barrier of rotation of **24** inside the cavity of (a) **2a** and (b) **4** calculated by force field (MMFF94).[29]

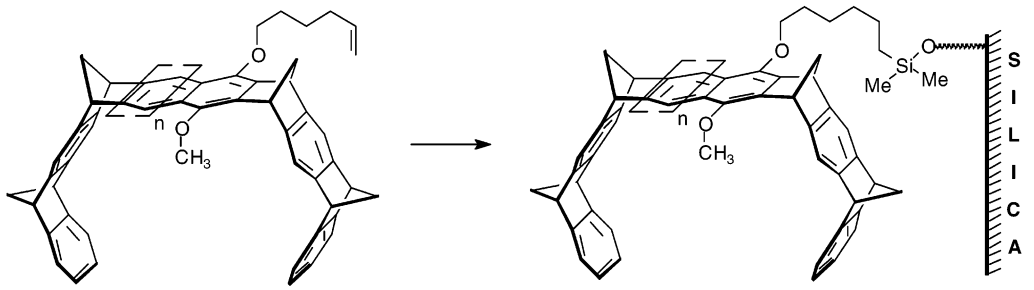


		24@2a	36@2b	24@4
$\Delta H^{\ddagger}$	=	13.2	8.6	9.5
$\Delta S^{\ddagger}$	=	-10.0	-13.4	-11.4
$\Delta G^{\ddagger}$	=	16.0	12.3	12.4
T [°C]	=	61.0	2.5	22.5

FIGURE 9. Activation parameters $\Delta H^{\ddagger}$ (kcal/mol), $\Delta S^{\ddagger}$ (cal mol^{-1} K^{-1}), and $\Delta G^{\ddagger}$ (kcal mol^{-1}) and temperature of coalescence T (°C) determined for the dissociation of the complexes **24@2a**, **36@2b**, and **24@4** from the temperature-dependent ^{1}H NMR spectra of 2:1 mixtures of **2a** and **24** in $(CDCl_2)_2$, **2b** and **36** (in $CDCl_3/CD_3OD$ (1:1)), and **4** and **24** (in toluene-d_8).[24,26,32]

such as TCNB **24** and $TrpBF_4$ **36**, which form stable complexes, separate signals of the 1:1 complexes and the excess of free receptors are observed at low temperatures.[24,26,32]

In these cases, the mutual complex formation and dissociation is slow with respect to the NMR time scale. An increase in temperature leads to a broadening and finally to a coalescence of these signals. From the lineshape analysis of the temperature-dependent spectra, the activation parameters for the dissociation of the three complexes shown in Figure 9 can be determined. The Gibbs activation enthalpies for the three complexes, $\Delta G^{\ddagger}$ = 16.0, 12.3, and 12.4 kcal/mol, respectively, are quite substantial. The finding of negative activation entropies for the dissociation processes seems to be surprising but can be understood by the calculation of the transition state of the dissociation of the complex **24@2a**. Accordingly, the substrate rotation inside the cavity has to be restricted, and the substrate is still clipped between the tweezer tips in the transition state of the complex dissociation. Both processes contribute negative terms to the entropy of activation. The finding that, in the complex **24@4**, the activation barriers of the substrate rotation inside the receptor cavity and of the complex dissociation are smaller by 3−4 kcal/mol than those in **24@2b** or **24@2a** can be explained by the more open topography of **4**.



1k (n=0)
2k (n=1)

CBSP-**1** (n=0)
CBSP-**2** (n=1)

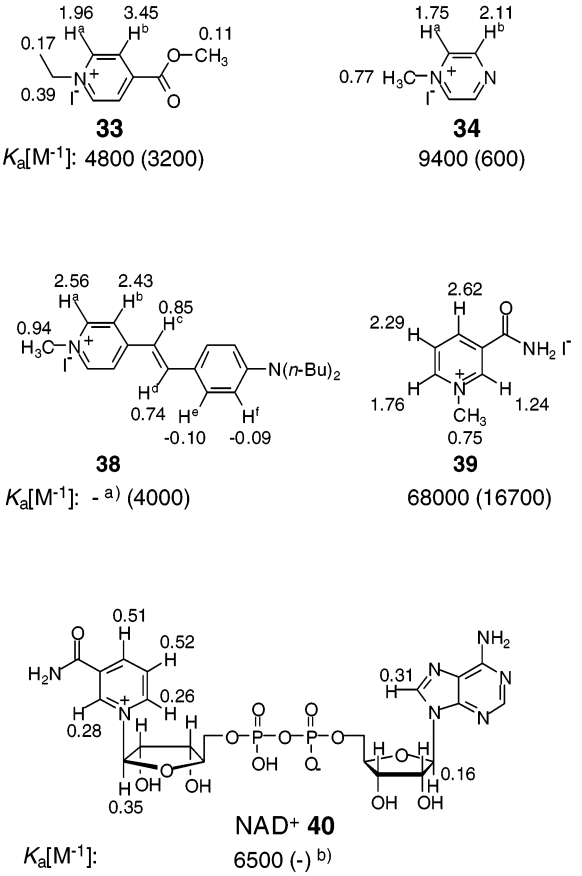
FIGURE 10. Molecular tweezers chemically bonded to a stationary HPLC phase.[33]

Solvent Dependence: The Complex Formation in Water

The solvent dependence of the complex formation was investigated with the molecular tweezers chemically bonded to a stationary HPLC phase, CBSP-**1** and CBSP-**2** (CBSP = chemically bonded to stationary phase) (Figure 10).[33] These two phases selectively retain electron-deficient aromatic and quinoid analytes of appropriate size and topography. The good qualitative correlation between the capacity factors k' derived from HPLC retention times and the association constants K_a obtained from the binding studies in solution using the molecular tweezer **1a** and **2a** as receptors[24] indicates that the mechanism of retention involves selective complexation by the molecular tweezers on the silica surface. The capacity factors k' and the absolute values of the enthalpy of retention (ΔH_R) (determined from the temperature dependence of k') are much larger in protic solvents (e.g., MeOH, EtOH, *i*-PrOH) and in nonpolar solvents (e.g., MTBE, CCl_4, cyclohexane) but substantially smaller in polar aprotic solvents (e.g., CH_3CN, DMF) than in $CHCl_3$.

This indicates that solvophobic effects might be the driving force for the binding in protic solvents. These conclusions are convincingly confirmed by a study with a water-soluble receptor. The dimethylene-bridged clip **5g** forms surprisingly stable complexes with *N*-alkylpyridinium salts in methanol and in aqueous solution (Figure 11).[34]

The observation that these complexes are more stable in water than in methanol is good evidence for the substantial contribution of the hydrophobic interaction in the receptor−substrate binding processes observed here and implies that, especially in water, it is the cation−π interaction and not the salt bridges that is largely responsible for the complex stability in accord with a computational study.[3] NAD^+, one of the most important redox coenzymes in nature, is also capable of forming a complex with **5g** in aqueous solution. The findings that the protons of both subunits (the nicotinamide as well as the adenine moiety) are shifted upfield in the ^1H NMR spectrum of NAD^+**40**@**5g** and that the $\Delta\delta_{max}$ values observed for the protons of the nicotinamide subunit are significantly smaller than those in **39**@**5g** indicate that at least two structures, including either the nicotinamide or the adenine subunit inside the cavity of **5g**, equilibrate rapidly on the NMR time scale. A Monte Carlo conformer search, leading to the energy-minimized double-sandwich structures shown in Figure 12, supports the experimental finding.



a) Broad signals in ^1H-NMR spectrum of **5g** and **38** in D_2O.
b) Precipitation of the complex after mixing **40** and **5g** in CD_3OD

FIGURE 11. ^1H NMR shifts, $\Delta\delta_{max}$, of the substrates **33**, **34**, and **38** in methanol, and **39** and **40** in water, and the association constants K_a (M^{-1}) in water (in methanol) of the complex formation with **5g** as receptor[34] (positive values of $\Delta\delta_{max}$ are upfield).

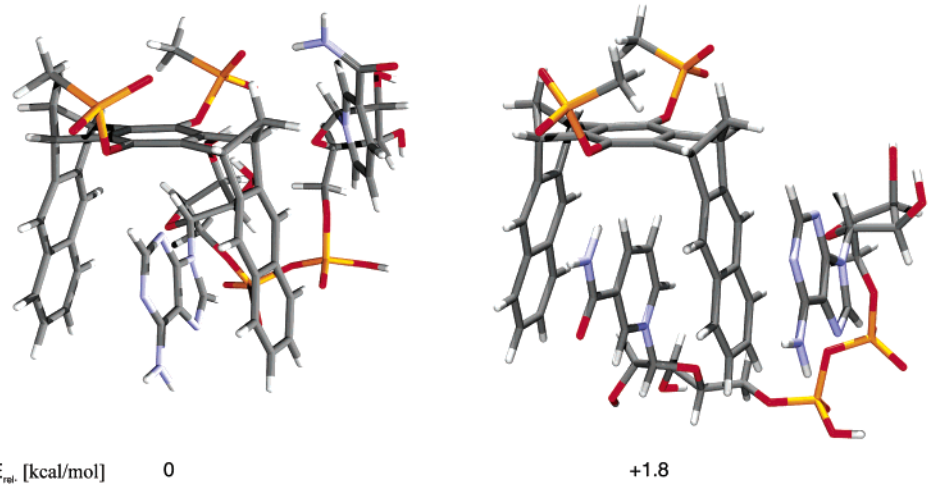
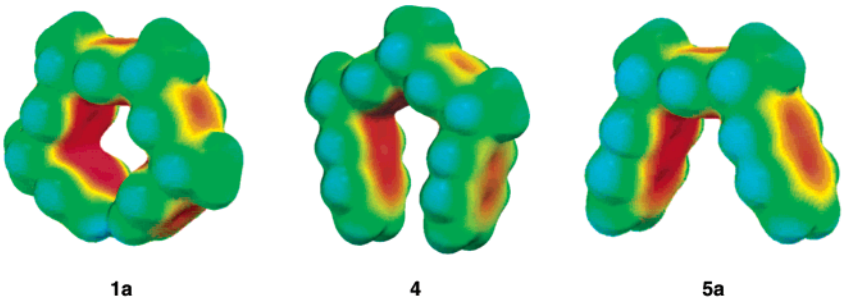


FIGURE 12. Structures of **NAD⁺40@5g** calculated by a Monte Carlo conformer search (5000 structures, Amber* (H_2O), MacroModel 7.0).[35]



	convex	concave	convex	concave	convex	concave
AM1	(-22)	(-35)	(-22)	(-34)	(-21)	(-31)
HF 6-31G*	(-28)	(-40)	(-28)	(-36)	(-23)	(-25)
DFT BP/DN**	(-44)	(-54)	(-43)	(-53)	(-40)	(-50)

FIGURE 13. EPS of **1a**, **4**, and **5a**. The results of the AM1 calculations are depicted. The color code spans from −25 (red) to +25 kcal/mol (blue). The most negative molecular electrostatic potential (MEP in kcal/mol) on each side of the molecules is given in parentheses.

Electrostatic Potential Surfaces as a Tool To Model Supramolecular Properties

The molecular tweezers and clips **1**−**7** serve as receptors for electron-deficient neutral and cationic substrates. No complex formation between these receptors and electron-rich aromatic, aliphatic, or anionic substrates can be detected. These findings, which are at first glance surprising, can be explained with the electrostatic potential surface (EPS) calculated by means of quantum-chemical methods (Figure 13). At all levels of theory employed here, the EPS was calculated to be surprisingly negative for pure hydrocarbons on the concave side of each molecule, whereas the EPS on the convex side is less negative, corresponding to that of tetraalkyl-substituted arenes such as durene. In Figure 13, the EPS and the molecular electrostatic potentials (MEPs) of the tweezer **1a** and clips **4** and **5a** are shown as representative examples.[36] When analogous calculations were performed for aromatic and aliphatic substrates which form complexes with the molecular tweezers and clips (Figure 14), the complementary nature of their electrostatic potential surface to that inside

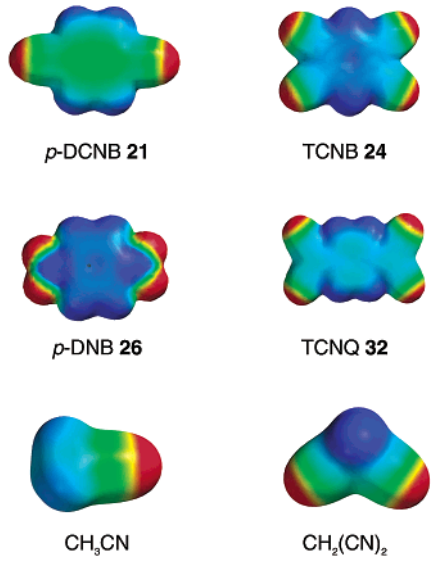


FIGURE 14. EPS calculated as AM1 for various aromatic and aliphatic substrates. The color code spans from −25 (red) to +25 kcal/mol (blue).

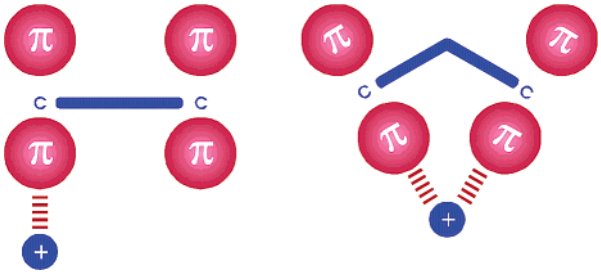


FIGURE 15. Schematic representation of the interaction of a positive test charge with nonconjugated "idealized" π-electron systems with linear (left) and concave geometry (right). The π-electron systems are negatively (red) charged, and the σ framework is positively (blue) charged.

the receptor cavities becomes evident, suggesting that the receptor−substrate interactions reported here for the tweezers and clips **1**−**7** are predominantly of electrostatic nature.

The results of the EPS calculations can be rationalized in the following way. The electrostatic potential at a certain site corresponds to the energy of interaction of a positive test charge with the wave functions of all nuclei and electrons of the investigated molecule and is inversely proportional to the distance of this site from the test charge (Figure 15). If two π-electron systems are linearly connected but not conjugated and the distance between them is large enough, the positive test charge at a position close to the first π system (Figure 15, left side) interacts only with the first π system and not with the second one, so that the electrostatic potential in this case is not influenced by the introduction of the second π system. However, if the molecule is bent, as is the case of the tweezers and clips, the two π systems at the same distance as in the first case (Figure 15, right side) approach each other on the concave side and the potential becomes more negative by the introduction of the second π system. This is a general phenomenon of all nonconjugated π systems having concave−convex topography, which, for example, also explains the binding properties of cyclophane-type receptors.[10,11]

Conclusions

The molecular tweezers and clips **1**−**7** serve as selective receptors for electron-deficient aromatic and aliphatic substrates. The complex structures have been elucidated with X-ray, NMR, and computational methods. In most complexes of the tweezers **2**, the plane of the aromatic substrates is aligned parallel to the central naphthalene spacer unit of **2**, whereas in the complexes of the clips **4**, **5**, and **7** the substrates are placed inside the receptor cavity with their molecular plane nearly parallel to the naphthalene or anthracene sidewalls and orthogonal to the central spacer unit. Evidently, attractive CH−π as well as π−π interactions contribute to the complex stability. EPS calculations suggest that these attractive receptor−substrate interactions are predominantly of electrostatic nature. The complex structures are, however, not rigid but quite flexible. The rotation of the noncovalently bound substrates inside the receptor cavities could be observed by temperature-dependent ^{1}H NMR measurements in solution and even in the solid state. This process is analogous to the rotation around a single C−C bond and, hence, can be considered to be the equilibration between noncovalent conformers.

The finding that the water-soluble clip **5g** forms stable complexes with *N*-alkylpyridinium ions, such as *N*-methylnicotinamide iodide **39** or NAD$^+$ **40**, which are more stable in aqueous solution than in methanol, is good evidence for the contribution of the hydrophobic effect to the receptor−substrate binding processes observed. These results are in good agreement with a systematic study of the solvent effect on the stability of the complex between a cyclophane receptor and pyrene as neutral substrate[37] and on the π−cation interactions in complexes between cyclophane receptors and various organic cations, such as aliphatic ammonium and aromatic pyridinium cations.[11,38] The clip **5g**, however, is a more selective receptor than the cyclophanes and does not bind, for example, aliphatic ammonium cations within the limits of NMR detection. Water-soluble derivatives of the tweezers **1** and **2** and the clips **4**−**7** are of great interest because they may serve as selective receptors for different classes of bioactive chemical substrates in aqueous solution. The synthesis of such derivatives is in progress.

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