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Donor/Acceptor-Substituted Chiral Molecular Clips – Synthesis and Host–Guest Complex Formation

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The synthesis, separation, and characterization of some substituted stereoisomeric dimethylene-bridged molecular clips bearing donor or acceptor groups at the tips of the naphthalene sidewalls and two acetoxy, hydroxy, or methoxy groups at the central benzene spacer unit are reported. The host–guest complex formation was studied for these substituted molecular clips as host molecules with 1,2,4,5-tetracyanobenzene (TCNB), *N*-methyl-*p*-(methoxycarbonyl)pyridinium iodide (Kosower's salt, KS), and *N*-methylnicotinamide iodide (NMNA) as guest molecules. The binding constants, K_a, and the complexation-induced ^{1}H NMR shifts of the guest signals, $\Delta\delta_{max}$, obtained by NMR titration experiments, are compared with those reported for the parent diacetoxybenzene, hydroquinone, or dimethoxybenzene clips. The diacetoxybenzene clip, bearing donor pyrrolidinyl groups at the tips of both naphthalene sidewalls, forms the most stable complexes with TCNB and KS, overwhelming the corresponding complexes of the parent clip and the clips bearing one nitro or methoxycarbonyl group at the tip of one naphthalene sidewall. The clips bearing two acceptor groups (two nitro or methoxycarbonyl groups) at the tips of both naphthalene sidewalls do not form any complex with TCNB, KS, or NMNA within the limits of NMR detection. The large complexation-induced ^{1}H NMR shifts of the guest signals provide good evidence that in each complex the guest molecule is clipped between the naphthalene sidewalls of the host molecule by attractive aromatic π–π and CH–π interactions, as suggested by force-field calculations. This structural assignment of the complexes is further confirmed by a single-crystal structure of the KS complex of the mono-nitro-substituted clip, which resembles the complex structure of the parent clip with KS. The good correlation between the clip's electrostatic potential surface (EPS; calculated by DFT for the donor- or acceptor-substituted molecular clips) and the host–guest complex stability confirms the assumption that in chloroform solution the host–guest binding (resulting from attractive aromatic π–π and CH–π interactions) is largely electrostatic in nature, whereas the EPS values do not correlate with the binding constants found in methanol solution, indicating that additional binding forces (resulting for example from solvophobic effects) contribute to the host–guest binding. The separated optically active diacetoxybenzene clips substituted by one or two methoxycarbonyl groups at the naphthalene sidewalls are a good starting point for future studies of chiral molecular recognition and organic catalysis.

Introduction

Efficient synthetic host molecules with the capability for selective binding of guest molecules play a key role in the design of higher organized chemical systems, which are important for the understanding of molecular recognition and self-assembly processes.[1] Recently, we have described the synthesis and some supramolecular properties of a family of host molecules termed molecular tweezers and clips that are well preorganized due to their belt-type concave–convex topography (Figure 1).[2] They preferentially bind electron-deficient aromatic and aliphatic guest molecules as well as organic cations inside the host cavity by using aromatic π–π and CH–π interactions as dominating noncovalent binding forces.[3] Electron-rich guest molecules are not bound by these molecular tweezers and clips. The high selectivity toward electron-poor guest molecules was explained with markedly negative electrostatic potential surfaces (EPS) calculated for the concave faces of these molecules, which are complementary to the positive electrostatic potential surfaces of the preferentially bound guest molecules.[4] This finding suggests that the host–guest binding in these complexes is predominantly electrostatic in nature.

In this work, we studied the effect of donor and acceptor substituents attached to the tips of the naphthalene sidewalls of dimethylene-bridged clips on the host–guest complex formation to gain further information on the noncovalent host–guest binding mode. We asked the question: how and to what extent is the host–guest complex stability correlated with the clip's EPS modulated by substituents. A computational study by Wheeler and Houk shows convincingly

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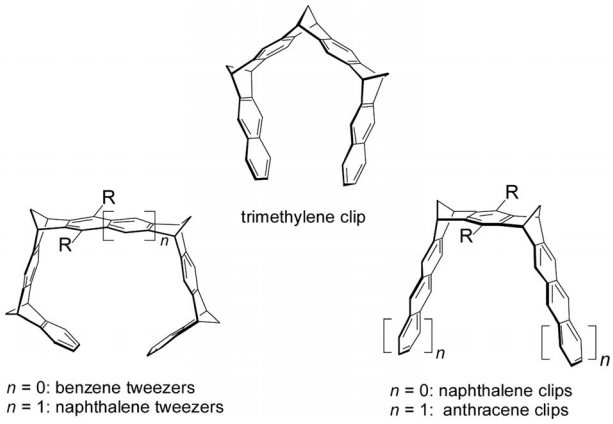


Figure 1. Structures of the tetramethylene-bridged tweezers and the tri- and dimethylene-bridged clips.

that significant changes in the EPS of aromatic systems arise from inductive through-space effects of substituents; π-resonance plays no discernible role.[5] Therefore, we selected the nitro and ester group as acceptors and the amino group as donor, which were already known to increase the positive or negative EPS of arene derivatives substituted with these groups.[5,6] In this work we synthesized the molecular clips **3**–**10** and **11**–**13** substituted by a nitro, ester, or amino function at the tip of naphthalene sidewalls and compared their supramolecular properties with those of the parent clips of type **1** (Figure 2).[7]

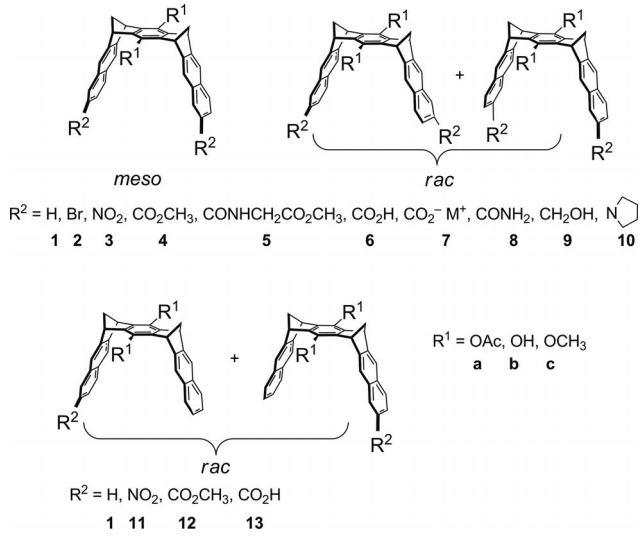


Figure 2. Dimethylene-bridged molecular clips bearing electron-donor and/or electron-acceptor substituents at the central benzene spacer unit and/or naphthalene sidewalls.

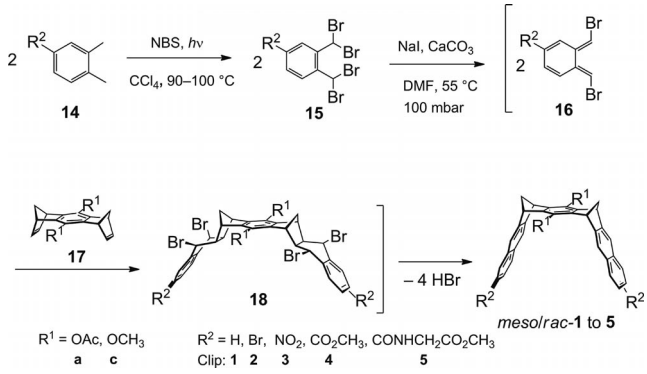
The molecular clips studied in this work are chiral. Compounds **2**–**10** exist in one *meso* and two enantiomeric configurations, and **11**–**13** in enantiomeric configurations only. The optically active stereoisomers of these compounds are certainly good candidates for future investigations of chiral molecular recognition and organic catalysis. Recently, we reported the synthesis and separation of chiral molecular clips of type **4a'** [R^1 = OAc, R^2 = CO_2(–)-menthyl].[8] One of the separated enantiomers showed a chiral discrimination toward D- and L-Trp-OMe·H^+ by a factor K_D/K_L = 3.5.

According to quantum-chemical calculations, multiple substitution of the benzene tweezer by acceptor groups such as fluorine, oxygen, or nitrile should lead to an "umpolung" of the EPS so that these compounds are expected to host anions.[9] In this work we synthesized the quinone clips *meso*/*rac*-**14** substituted by nitro groups at the tips of naphthalene sidewalls. The EPS of *meso*-**14** (Figure 9) is calculated to be relatively positive inside the clip cavity compared to the rest of the clip molecules studied in this work. However, a 1:1 mixture of *meso*/*rac*-**14** binds neither electron-rich guest molecules (such as aminobenzene derivatives or phenolates) nor electron-poor guest molecules (Scheme 6). Evidently, binding of anions by these types of host molecules needs a further increase in the positive EPS by the introduction of additional acceptor groups as substituents.

Results and Discussion

Synthesis of Chiral Molecular Clips Disubstituted at the Tips of the Naphthalene Sidewalls

The synthesis of substituted naphthalene clips **2a**,**c**–**5a**,**c** was performed by a method analogous to that used for the parent naphthalene clips **1a**,**c** (R^1 = OAc, OMe; R^2 = H).[7] *N*-Bromosuccinimide (NBS) mediated bromination of the *o*-xylene derivatives **14** substituted at C-4 by a bromo, nitro, or methoxycarbonyl group (R^2 = Br, NO_2, or CO_2CH_3) led to the corresponding tetrabromo-*o*-xylene derivatives **15** in yields of 54, 80, and 80%, respectively. The *N*-benzoylglycine methyl ester derivative **15** (R^2 = $CONHCH_2CO_2CH_3$) was prepared by the NBS-mediated bromination of 3,4-dimethylbenzoyl chloride **14** (R^2 = COCl, yield: 70%) followed by reaction with 3,4-bis(dibromo)methylbenzoyl chloride **15** (R^2 = COCl) and the HCl adduct of glycine methyl ester (H_3N^+–CH_2–CO_2CH_3 Cl^-) in the presence of triethylamine in tetrahydrofuran (THF) at 0 °C (yield: 90%). The *meso*/*rac* mixture of the clips **2a**, **2c**, **3a**, **3c**, **4a**, **4c**, or **5c** was synthesized in a one-pot reaction starting with the 1,4-elimination of bromine from the corresponding substituted tetrabromo-*o*-xylene derivative **15** by sodium iodide, leading to the dibromo-*o*-quinodimethane derivatives **16** as transient intermediates, which react as dienes with the benzonorbornadiene derivatives **17** as bisdienophiles in repetitive Diels–Alder reactions leading to the bis-adducts **18** (Scheme 1). Compounds **18** are not stable under the conditions of the reaction and spontaneously eliminate four equivalents of hydrogen bromide leading to the desired molecular clip as mixtures of the corresponding *meso*- and *rac*-isomers. The yields and product ratios are given in Table 1.



Scheme 1. General scheme for the synthesis of molecular clips (disubstituted at the naphthalene sidewalls): Repetitive Diels–Alder reactions of benzonorbornadiene derivatives **17** as bisdienophile with *o*-quinodimethane derivatives **16** as diene produce cycloadducts of type **18**, which undergo subsequent HBr elimination under the reaction conditions employed leading to the molecular clips *meso*/*rac*-**1** to **5**. The *o*-quinodimethane derivatives **16** are generated in situ from tetrabromo-*o*-xylene derivatives **15** by 1,4-Br_2 elimination. The tetrabromo-*o*-xylenes **15** are prepared by NBS mediated bromination of the corresponding *o*-xylenes **14** (NBS = *N*-bromosuccinimide; DMF = *N*,*N*-dimethylformamide).

Table 1. Product ratios and yields of molecular clips **2**–**5** synthesized by the route shown in Scheme 2.

R^1	R^2	Product ratio	Yield [%]
OAc	Br	*meso*/*rac*-**2a** (3:2)	60
OCH_3	Br	*meso*/*rac*-**2c** (3:2)	50
OAc	NO_2	*meso*/*rac*-**3a** (1:1)	20
OCH_3	NO_2	*meso*/*rac*-**3c** (1:1)	58
OAc	CO_2CH_3	*meso*/*rac*-**4a** (1:1)	80
OCH_3	CO_2CH_3	*meso*/*rac*-**4c** (1:1)	93
OCH_3	$CONHCH_2CO_2CH_3$	*meso*/*rac*-**5c** (1:1)	76

The product mixtures (Table 1) could be separated by liquid chromatography into the corresponding *meso* and *racemic* isomers, in the case of *meso*/*rac*-**2a** and *meso*/*rac*-**2c** by HPLC on a column packed with achiral silica gel [Knauer Eurospher 100 Si, eluted with *n*-hexane/*tert*-butyl methyl ether (85:15)] and in the case of *meso*/*rac*-**3a**, *meso*/*rac*-**3c**, *meso*/*rac*-**4c**, and *meso*/*rac*-**5c** by MPLC (medium-pressure liquid chromatography) on silica gel with ethyl acetate/*n*-heptane eluent of varying ratios. The MPLC separation of *meso*/*rac*-**5c** is shown in Figure 3 as a representative example.

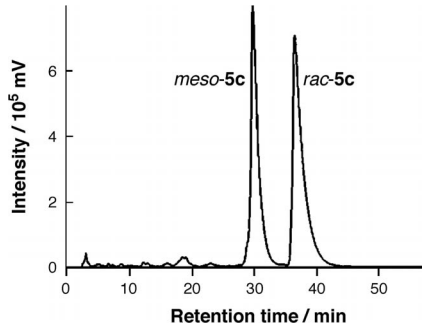


Figure 3. MPLC separation of *meso*/*rac*-**5c** on silica gel with ethyl acetate as an eluent.

The mixture of ester-substituted clips *meso*/*rac*-**4a** did not show any separation under the chromatographic conditions mentioned above. However, this mixture could be separated into *meso*-**4a** and enantiomeric (+)-**4a** and (–)-**4a** by chiral HPLC on a Chiralcel OD column (*n*-heptane/2-propanol, 75:25; Figure 4, left), as was the case with the related, previously published, optically active (–)-menthyl ester-substituted clips **4a′** [R^1 = OAc, R^2 = CO_2(–)-menthyl].[8] The separated optically active enantiomers were assigned on the basis of their mirror-imaged CD spectra as (+)-**4a** and (–)-**4a** (Figure 4, right).

The syntheses of the derivatives *meso*/*rac*-**6c**, **-6b**, **-8c**, **-8b**, or **-9b** starting from the diacetoxybenzene or dimethoxybenzene clips *meso*/*rac*-**3a**, **-4a**, or **-4c** are summarized in Schemes 2 and 3. Base-mediated hydrolysis either of the mixture or of the separated *meso*-**3a** and *rac*-**3a** led to the dinitro-substituted hydroquinone clips *meso*-**3b** and *rac*-**3b**. The mixture of *meso*/*rac*-**3b** was oxidized with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to the corresponding quinone clips *meso*/*rac*-**14** (Scheme 2). The hydroquinone

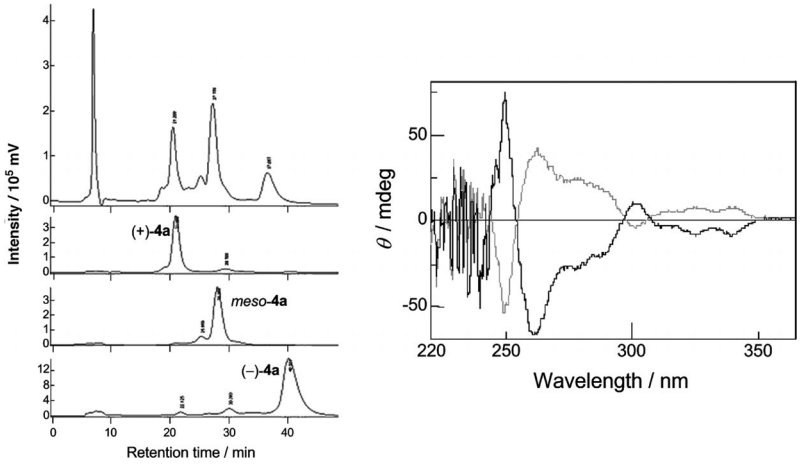
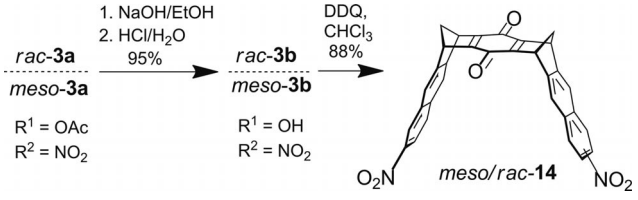
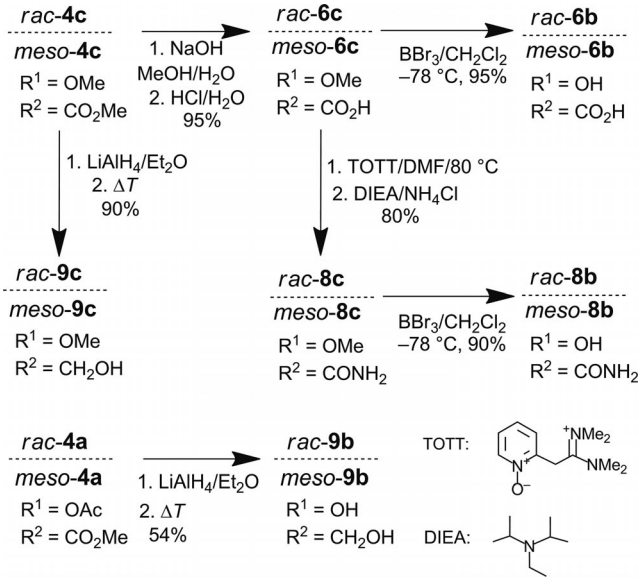


Figure 4. Left: HPLC chromatograms of mixtures of *meso*/*rac*-**4a** (top) and of the separated stereoisomers (+)-**4a**, *meso*-**4a**, (–)-**4a** (Chiralcel OD; *n*-heptane/2-propanol, 75:25). Right: CD spectra of the separated (+)-**4a** (black) and (–)-**4a** (light grey) in 2,2,2-trifluoroethanol.

clips *meso*/*rac*-**6b** and *meso*/*rac*-**8b**, bearing carboxylic acid or amide functions at the naphthalene sidewalls, were prepared in two and three steps, respectively, starting from the methoxybenzene clips *meso*/*rac*-**4c** (Scheme 3). The methoxy group of the dicarboxylic acid *meso*/*rac*-**6c** (obtained from *meso*/*rac*-**4c** by saponification) were cleaved with BBr_3, leading to the corresponding hydroquinone clips *meso*/*rac*-**6b**. Aminolysis of the carboxylic acid groups of *meso*/*rac*-**6c** and subsequent cleavage of the methoxy groups with BBr_3 gave the desired hydroquinone clips *meso*/*rac*-**8b**. The ester groups of *meso*/*rac*-**4c** were reduced with lithium aluminum hydride to produce the dimethoxybenzene clips *meso*/*rac*-**9c** substituted with hydroxymethyl groups at the naphthalene sidewalls, whereas all ester groups of *meso*/*rac*-**4a** were reduced with lithium aluminum hydride leading to the hydroxymethyl-substituted hydroquinone clips *meso*/*rac*-**9b**.

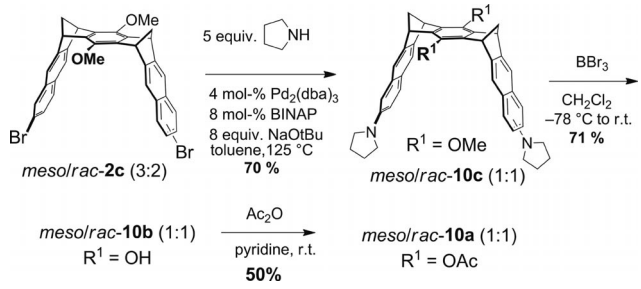


Scheme 2. Synthesis of the hydroquinone and quinone clips *meso*/*rac*-**3b** or -**14**, each bearing nitro-substituents at the naphthalene sidewalls, starting from the diacetoxybenzene clips *meso*/*rac*-**3a**.



Scheme 3. Synthesis of the molecular dimethoxybenzene clips *meso*/*rac*-**6c**, -**8c** and hydroquinone clips *meso*/*rac*-**6b**, -**8b**, and -**9b**, bearing carboxyl, amide, and hydroxymethyl groups at the naphthalene sidewalls, by selective transformation of the methoxy or acetoxy groups of the central spacer unit as well as the methoxycarbonyl groups at the naphthalene sidewalls in *meso*/*rac*-**4c** and *meso*/*rac*-**4a**, respectively.

The donor-substituted dimethoxybenzene clips *meso*/*rac*-**10c** bearing pyrrolidinyl groups at the tips of the naphthalene sidewalls were prepared by palladium-catalyzed substitution of the bromide functions in the molecular clips *meso*/*rac*-**2c** with pyrrolidine.[10] Cleavage of the methoxy groups of *meso*/*rac*-**10c** with BBr_3 produced the corresponding hydroquinone clips *meso*/*rac*-**10b**, which were converted by reaction with acetic anhydride into diacetoxy derivatives *meso*/*rac*-**10a** (Scheme 4).



Scheme 4. Synthesis of the dipyrrolidinyl-substituted molecular clips *meso*/*rac*-**10c**,**b**,**a**. [$Pd_2(dba)_3$] = tris(dibenzylideneacetone)dipalladium(0), BINAP = *rac*-2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl.

The structures of the new clip molecules were assigned on the basis of their spectra. As a consequence of the molecular symmetry, the ^1H NMR spectra of the separated *meso* and *racemic* diastereomers of the diacetoxybenzene- or dimethoxybenzene-substituted clips **3a**,**c**, **4a**,**c**, and **5c** are clearly different from each other. The two $O(CO)CH_3$ groups or the two OCH_3 groups in each *meso*-configured clip are not equivalent, giving two separate sets of ^1H NMR signals for the methyl protons, whereas the same protons of the corresponding racemate or optically active clip only show a single signal, in agreement with its symmetry. This assignment was confirmed in the case of the separated clips *meso*-**4a**, (+)-**4a**, and (–)-**4a** by their CD spectra (Figure 4) and, in the case of *meso*-**5c**, by X-ray analysis (Figure 5). The single-crystal structure of *meso*-**5c** shows an unusually short distance of 6.9 Å between the tips of the naphthalene sidewalls compared to the distance of 11.4 Å found in the single-crystal structure of clip **1a**.[6] The compression of

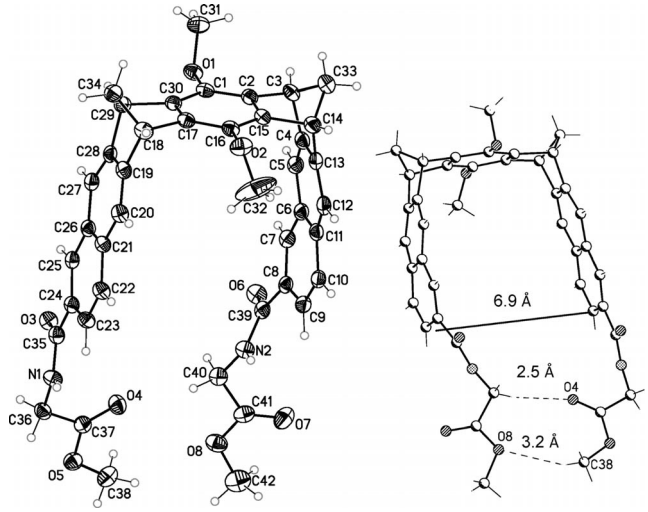


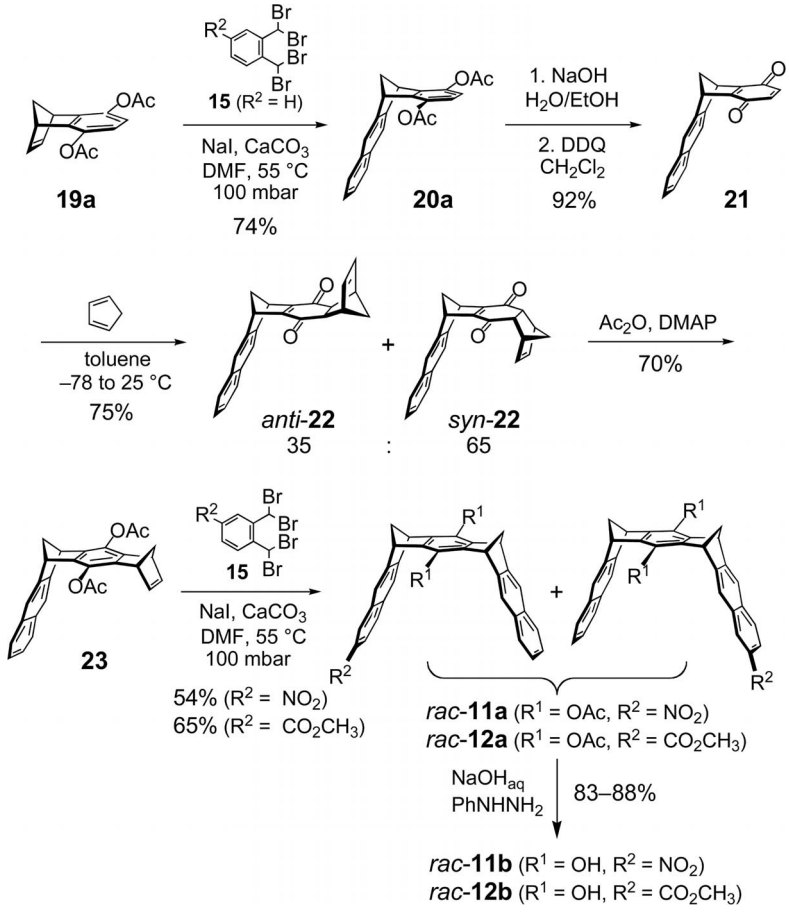
Figure 5. Single-crystal structure of *meso*-**5c**.

the sidewalls in *meso*-**5c** evidently results from the weak intramolecular CH···O hydrogen bonds between the $CONHCH_2CO_2CH_3$ substituents (Figure 5).

Synthesis of Chiral Molecular Clips Monosubstituted at the Tip of One Naphthalene Sidewall

We first attempted to prepare molecular clips of type **11** or **12** (*mono*-substituted at the tip of one naphthalene sidewall) by conducting the reaction with equimolar amounts of bisdienophile **17a** and tetrabromo-*o*-xylene **15** (R^2 = H). This reaction, however, led to a complex mixture of products containing, beside the desired 1:1 adduct **23**, the 1:2 adduct (clip **1a**) and unreacted **17a**, which was difficult to separate. A rational synthesis of these clips began with the preparation of the naphtho-substituted dienophile **23**. The Diels–Alder reaction of 1,3-cyclopentadiene with the known quinone **21** (accessible from benzonorbornadiene **19a** in two steps as shown in Scheme 5)[11] gave a 65:35 mixture of *syn*- and *anti*-**22**, which was easily separated by MPLC. The reaction of **23** (resulting from base-mediated enolization and acetylation of the keto function in *syn*-**22**) with the tetrabromo-*o*-xylene derivatives **15** (R^2 = CO_2CH_3 or NO_2) led to the racemate of the desired mono-nitro- or mono-methoxycarbonyl-substituted clips *rac*-**11a** or *rac*-**12a** (Scheme 5). Saponification of *rac*-**11a** and *rac*-**12a** with sodium hydroxide in the presence of phenylhydrazine at room temperature gave the corresponding hydroquinone clips *rac*-**11b** and *rac*-**12b** in almost quantitative yields. In the case of *rac*-**12a**, the acetyl functions were also selectively hydrolyzed in the presence of the methoxycarbonyl groups under these conditions.

The structures of the new molecular clips were assigned on the basis of their spectra. The ^{1}H NMR spectra of the hydroquinone clips *rac*-**11b** and *rac*-**12b** are concentration-dependent, the signals assigned to the protons attached to naphthalene sidewalls were shifted toward larger δ values upon dilution (see Figures S2 and S3 in the Supporting Information), indicating that these clips form weak dimers that are comparable to molecular clips with extended aromatic sidewalls.[12] The enantiomers of the methoxycarbonyl-substituted clip **12a** could again be separated by HPLC on a chiral column (Figure 6, left). The separated enantiomers (+)-**12a** and (–)-**12a** showed the expected mirror-imaged CD spectra (Figure 6, right).



Scheme 5. Synthesis of racemic molecular clips (monosubstituted at the tip of one naphthalene sidewall). DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMAP = 4-(dimethylamino)pyridine.

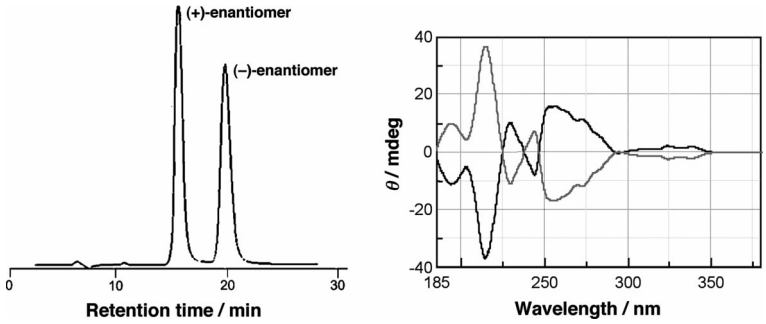
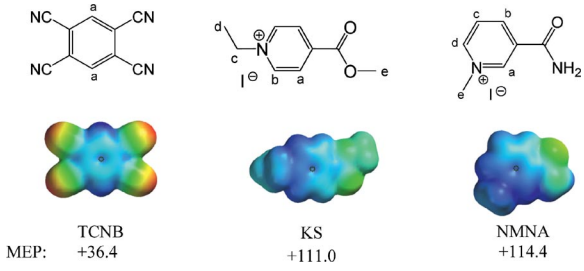


Figure 6. Left: HPLC chromatogram of the mixture of *rac*-**12a** (Chiralcel OD; *n*-heptane/2-propanol 75:25). Right: CD spectra of the separated enantiomers (+)-**12a** (grey) and (–)-**12a** (black) in 2,2,2-trifluoroethanol.

Host–Guest Complex Formation; Structural and Thermodynamic Parameters

The magnetic anisotropy of the clip arene units makes ^{1}H NMR spectroscopy a sensitive probe for uncovering the binding of a guest molecule inside the clip cavity. The host–guest complex formation can be easily detected by pronounced upfield shifts of the ^{1}H NMR signals of the guest protons (toward smaller δ values) upon addition of the clip as host molecule. In all binding processes reported here the host–guest association and dissociation are fast processes with respect to the NMR timescale. Thus, the maximum complexation-induced ^{1}H NMR shifts, $\Delta\delta_{max}$, of the guest signals and the binding constants, K_a, could be determined by ^{1}H NMR titration ($\Delta\delta_{max} = \delta_0 - \delta_C$; where δ_0, δ_C are the chemical shifts of the protons of the free and complexed guest molecule, respectively). In these experiments the dependence of the complexation-induced ^{1}H NMR shifts, $\Delta\delta_{obs}$, of the guest signals on the host concentration, $[H]_0$, at a constant guest concentration, $[G]_0$ = fixed, is measured as described in the Exp. Section ($\Delta\delta_{obs} = \delta_0 - \delta_{obs}$, where δ_{obs} is the chemical ^{1}H NMR shift of the guest proton observed in the presence of the host molecule and, hence, the weighted average between δ_0 and δ_C).[13] The complex formation between the parent diacetoxy- or dihydroxy-substituted clip **1a** or **1b** and TCNB as guest molecule was also detected by the observation of a new absorption band at λ_{max} = 416 nm in the UV/Vis spectra of equimolar mixtures of **1a** or **1b** and TCNB in $CHCl_3$ solution, which was assigned to the charge-transfer band of the host–guest complex TCNB·**1a** and TCNB·**1b**, respectively.

In this work, we investigated the potential host–guest complex formation of TCNB, KS, and NMNA as guest molecules (Scheme 6) with the acceptor-substituted molecular clips **3a**,**b**, **4a**,**b**, **11a**,**b**, and **12a**,**b** and the donor-substituted clips **10a**,**c** in two solvents, chloroform and methanol. The results are shown in Table 2 and Table 3; the ultimate chemical shifts upon complexation (δ_C) and, hence, the $\Delta\delta_{max}$ values were determined by the least-squares fits of the NMR titration data (see the Supporting Information). The molecular clips **11a**, **12a** and **11b**, **12b** (monosubstituted with a nitro or methoxycarbonyl acceptor group at the tip of one naphthalene sidewall) formed host–guest complexes with all three guest molecules, whereas no complex formation was found for the molecular clips **3a**, **3b** and **4a**, **4b** (disubstituted with these acceptor groups) within the limits of ^{1}H NMR detection. However, molecular clips **10a** and **10c** (disubstituted with the donor pyrrolidinyl groups) formed stable complexes with TCNB and KS.



Scheme 6. Structures and electrostatic potential surface (EPS), calculated by DFT using structures optimized by AM1 (B3LYP/6-31G**//AM1)[16] of the guest molecules: 1,2,4,5-tetracyanobenzene (TCNB), *N*-methyl-*p*-(methoxycarbonyl)pyridinium iodide (Kosower's salt, KS), and *N*-methylnicotinamide iodide (NMNA). The color code ranges from –30 (red) to +45 kcal/mol (blue) for TCNB, and from –30 (red) to +125 kcal/mol (blue) for the pyridinium salts: KS and NMNA. The listed molecular electrostatic potentials (MEP in kcal/mol) were calculated at the marked positions.

The large $\Delta\delta_{max}$ values of the guest protons determined for the complexes of the substituted molecular clips (see Tables 2 and 3) are of comparable size to those found for complexes of the parent clips **1a** and **1b**.[6] These findings indicate that the substituents attached to the naphthalene sidewalls have no significant effect on the complex structures and that, in each complex, the guest molecule is bound inside the clip cavity as shown by the single-crystal structures of the complexes of KS as a guest molecule and the diacetoxybenzene clip **1a**[7] or its nitro-substituted derivative **3a** as host molecules (Figure 7).

The experimentally determined complex structures agree well with structures predicted by force field calculations (MMFF 94).[14] In all structures the aromatic ring of the guest molecule (TCNB, KS, or NMNA) is calculated to be clipped between the naphthalene sidewalls of the host molecule (Figure 8). In the host–guest complex structures the protons attached to the benzene ring of TCNB or to the aromatic ring of KS are no longer equivalent to each other, pointing either towards the central spacer unit or to the

Table 2. Binding constants K_a [M^{-1}] and maximum complexation-induced ^1H NMR shifts of the guest signals $\Delta\delta_{max}$ [ppm] ($\Delta\delta_{max} = \delta_0 - \delta_C$, where δ_0 and δ_C are the chemical shifts of free and complexed guest protons, respectively) determined for the host–guest complex formation of molecular clips as host molecules and TCNB or KS as guest molecules by ^1H NMR titration experiments performed in $CDCl_3$ at 25 °C.

Host	Guest: TCNB		Guest: KS					
	K_a	$\Delta\delta_{max}$	K_a	$\Delta\delta_{max}$				
		H^a		H^a	H^b	H^c	H^d	H^e
R^1 = OAc								
1a: R^2 = H	140 ± 14[a]	3.4	137 ± 14[a]	1.8	2.4	1.6	–	–
11a: R^2 = NO_2	36 ± 5	2.1	41 ± 5	1.0	2.1	1.2	0.8	–0.1
3a: R^2 = NO_2	–	–	< 10	–				
12a: R^2 = CO_2CH_3	45 ± 5	3.6	60 ± 10	1.0	1.7	1.1	0.7	–
4a: R^2 = CO_2CH_3	–	–	< 10	–				
10a: R^2 = $N(C_4H_8)$	780 ± 110	4.1	1380 ± 140	1.7	2.2	1.7	1.1	0.03
R^1 = OH								
1b: R^2 = H	2180 ± 200[a]	3.6	1080 ± 110[a]	2.8	2.4	–	–	–
11b: R^2 = NO_2	precipitation		1045 ± 10	1.2	1.3	0.3	0.1	–0.9
3b: R^2 = NO_2	–	–	< 10	–				
12b: R^2 = CO_2CH_3	270 ± 30	3.6	1760 ± 180	3.5	2.3	0.9	1.0	–
4b: R^2 = CO_2CH_3	–	–	–	–				
R^1 = OMe								
1c: R^2 = H	< 7[a]	–	not determined					
10c: R^2 = $N(C_4H_8)$	214 ± 14	3.5	117 ± 2	2.1	2.4	1.3	0.9	0.2

[a] Ref.[7]

Table 3. Binding constants K_a [M^{-1}] and maximum complexation-induced ^1H NMR shifts of the guest signals $\Delta\delta_{max}$ [ppm] ($\Delta\delta_{max} = \delta_0 - \delta_C$, where δ_0 and δ_C are the chemical shifts of free and complexed guest protons, respectively) determined for the host–guest complex formation of molecular clips as host molecules and NMNA or KS as guest molecules by ^1H NMR titration experiments performed in CD_3OD at 25 °C.

Host	Guest: NMNA						Guest: KS					
	K_a	$\Delta\delta_{max}$					K_a	$\Delta\delta_{max}$				
		H^a	H^b	H^c	H^d	H^e		H^a	H^b	H^c	H^d	H^e
R^1 = OAc												
1a: R^2 = H	109 ± 11[a]	2.5	3.3	3.5	2.1	2.7	–	–				
12a: R^2 = CO_2CH_3	190 ± 14	1.3	1.8	2.0	1.2	1.4	143 ± 14	1.9	2.2	1.4	1.0	–
4a: R^2 = CO_2CH_3	–	–					–	–				
11a: R^2 = NO_2	125 ± 5	1.0	1.3	1.6	1.1	1.1	82 ± 10	1.2	1.4	0.9	0.7	–
3a: R^2 = NO_2	< 10	–					–	–				
R^1 = OH												
1b: R^2 = H	251 ± 30	1.0	2.6	1.6	1.1	0.8	280 ± 30	2.7	2.5	0.8	0.3	–
12b: R^2 = CO_2CH_3	150 ± 15	0.9	2.3	1.4	1.0	–	380 ± 15	1.5	1.4	0.5	0.2	–
4b: R^2 = CO_2CH_3	–	–					–	–				
11b: R^2 = NO_2	320 ± 40	1.1	2.3	1.9	1.9	0.8	170 ± 20	0.8	0.9	0.6	0.4	–
3b: R^2 = NO_2	< 10	–					–	–				

[a] Determined in $CD_3OD/CDCl_3$ (7:1); B. Rademacher, F.-G. Klärner, unpublished results.

open end of the clip molecule. Thus, separate signals are expected for these protons in the ^1H NMR spectra of the complexes. The observation of only one shifted ^1H NMR guest signal for each TCNB complex and two guest signals for each KS complex is good evidence for dynamic complex structures, which means that the rotation of the guest molecule inside the clip cavity and the mutual host–guest association and dissociation are fast processes with respect to the NMR timescale. Thus, in each complex, the observed NMR signals of these protons are averaged, which is comparable to the corresponding host–guest complexes of the tetramethylene-bridged tweezers and trimethylene-bridged clips, for which separate signals for the guest protons were observed at very low temperature.[15]

The TCNB and KS complexes of the diacetoxybenzene clips in chloroform solution show a clear sequence in their stability depending on the donor and acceptor substituents at the naphthalene sidewalls. The molecular clip **10a** (substituted with two pyrrolidinyl donor groups) forms the most stable complexes, whereas no complex formation was detected for the clips **3a** or **4a** (each substituted with two nitro or two methoxycarbonyl acceptor groups). The complexes of the monosubstituted clips **11a** and **12a** are less stable than those of the parent clip **1a**. The following sequences of decreasing stability were found: TCNB·**10a** > TCNB·**1a** > TCNB·**12a** ≈ TCNB·**11a** > TCNB·**4a**, TCNB·**3a** and KS·**10a** > KS·**1a** > KS·**12a** ≈ KS·**11a** > KS·**4a**, KS·**3a** (Table 2). The finding that the TCNB and KS complexes of

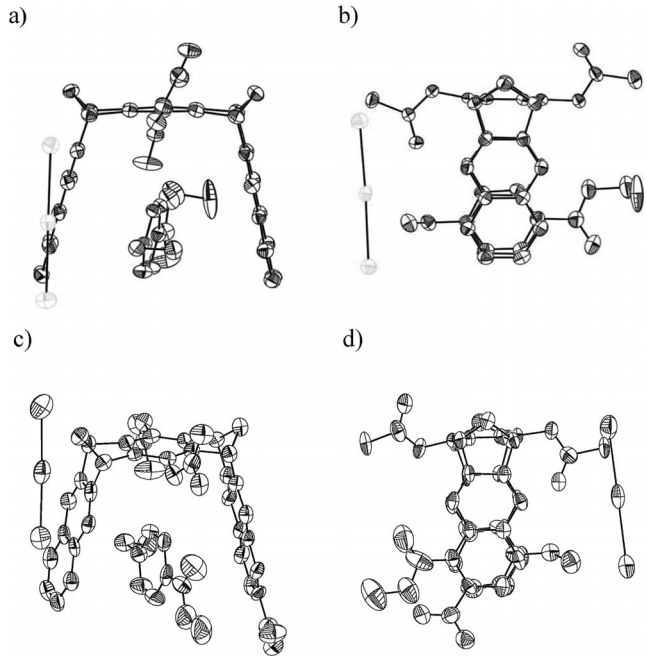


Figure 7. Single-crystal structures of host–guest complexes of KS (counterion: I_3^- instead of I^-) with the parent clip **1a** [(a) front view, (b) side view],[7] and of the mono-nitro-substituted clip **11a** [(c) front view, (d) side view].

the hydroquinone clip **1b** in chloroform solution are more stable than the corresponding complexes of **1a**, was already explained with the OH functions in **1b** binding the guest molecules by OH···N hydrogen bonds in addition to the aromatic π–π and CH–π interactions.[6] Evidently, the complexes of monosubstituted clips **11b** and **12b** are also substantially stabilized by these hydrogen bonds. The KS complex of methoxycarbonyl-substituted clip **12b** is even more stable than that of clip **1b** and the complex of the nitro-substituted clip **11b** is as stable as that of clip **1b** (Table 2). However, the hydroquinone clips **3b** and **4b** (each substituted with two acceptor groups) did not show any complex formation with TCNB or KS as guest molecule within the limits of NMR detection comparable to the diacetoxybenzene clips **3a** and **4a**. The dimethoxybenzene clip **1c** was already known to be a very weak binder.[6] The methoxy groups in **1b** were calculated by force field computations to point toward the clip cavity in the lowest energy conformation so that these groups have to rotate while the guest molecule enters the clip cavity. This conformational change costs additional energy. The donor groups in **10c** apparently more than compensate for the disadvantage associated with the methoxy groups so that the complex formation of **10c** with TCNB and KS is observed. However, the complexes TCNB·**10c** and KS·**10c** are significantly less stable than TCNB·**10a** and KS·**10a**. In methanol solution the dependence of the complex stabilities on the substituents is less pronounced (Table 3). The molecular clips **3a**, **4a** and **3b**, **4b** (each substituted with two acceptor groups) also show no complex formation with NMNA and KS as guest molecules in methanol. It is remarkable that the complexes of the hydroquinone clips **1b** and **12b** are substantially less stable in methanol than in chloroform. This observation supports the assumption that the hydrogen bonds contribute significantly to complex stability in chloroform. These bonds are less important in the protic solvent methanol.

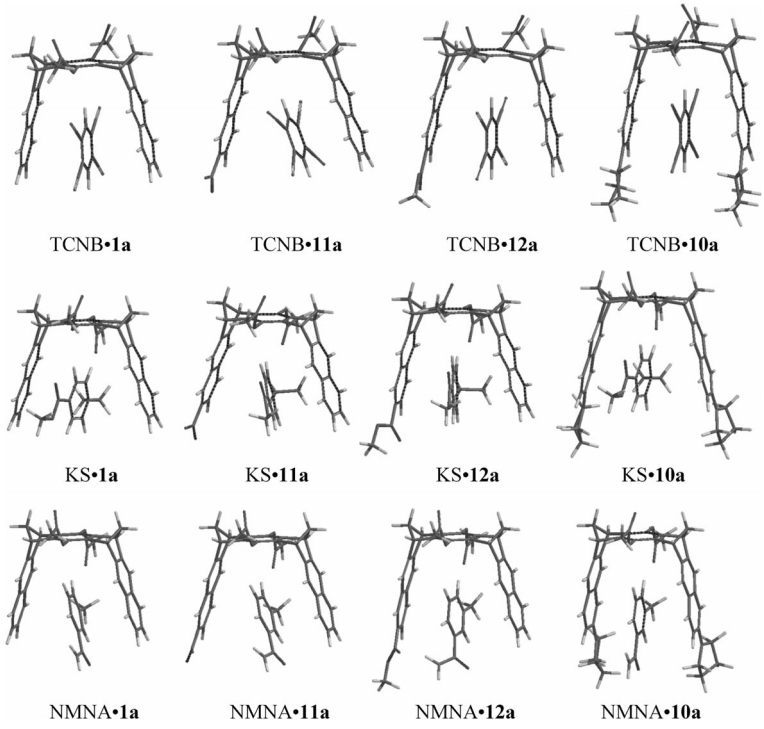


Figure 8. Structures of host–guest complexes calculated by force field computations (MMFF 94).

Finally, we calculated the electrostatic potential surface values (EPS) of the molecular clips to answer the question that was posed in the introduction: whether or not the clip's EPS modulated by the donor or acceptor substituents is correlated with the host–guest complex stability. Thus, the EPS values of the clips (Figure 9) were calculated by DFT using the structures optimized by AM1.[16] The EPS of the aromatic rings of the clip molecules (Figure 9) were calculated to be all negative and, hence, complementary to the positive EPS of the guest molecules (Scheme 6). An exception is the quinone clip *meso*-**14**, which shows a slightly positive EPS for its aromatic rings (Figure 9). According to the experimentally determined and calculated complex structures, the aromatic ring of each guest molecule is clipped between the terminal benzene rings of the naphthalene sidewalls. Thus, certainly the aromatic host–guest π–π interactions between these rings contribute to the host–guest binding in addition to the aromatic CH–π interaction between the guest molecule and the central aromatic clip spacer unit. Therefore, the molecular electrostatic potentials (MEP) were calculated at the marked positions in the center of the peripheral benzene rings (Figure 9) as well as in the center of the aromatic spacer unit (see the Supporting Information, Figure S1). The changes in the MEP values (caused by these substituents) calculated for central benzene rings (ranging from –21.0 kcal/mol for *meso*-**10a** to –4.3 kcal/mol for *meso*-**3a**, Figure S1) are similar to those calculated for the peripheral benzene rings (ranging from –24.3 for *meso*-**10a** to –4.5 kcal/mol for *meso*-**3a**, Figure 9).

Indeed, the stabilities of the complexes of diacetoxybenzene clips **1a**, **3a**, **4a**, **10a**, **11a**, and **12a** with the guest molecules TCNB and KS in chloroform solution correlate well with the MEP values shown in Figure 9 and Figure S1. In Figure 10, the $\log K_a$ values obtained for the complexation of TCNB, KS, and NMNA with **1a**, **10a**, **11a**, and **12a** in $CDCl_3$ and CD_3OD are plotted against the sum of the products of –MEP(host) and MEP(guest), i.e., $-\Sigma MEP(H)_i$-MEP(G) (i = 1–2, corresponding to each of the host's peripheral aromatic rings), as a measure of the electrostatic interactions between host and guest. Although the $\log K_a$ value is not rigorously proportional to the $\Sigma MEP(H)_i$-MEP(G) value even in $CDCl_3$, the donor-disubstituted clip **10a**, showing the most negative MEP values, forms the most stable host–guest complexes, whereas monosubstituted clips **11a** and **12a** (showing different MEP values at the unsubstituted and substituted peripheral aromatic ring) forms complexes that are less stable than those of unsubstituted clip **1a**. Finally, the acceptor disubstituted clips **3a** and **4a**, which do not form host–guest complexes, show the least negative MEP values. In methanol there is not such a clear correlation between the MEP values of the clips and the binding constants K_a, but also in this solvent the acceptor disubstituted clips **3a**,**b** and **4a**,**b** do not show any tendency to bind the guest molecules NMNA and KS. This finding suggests that, in protic solvents, forces other than electrostatic interactions, for example the solvophobic effects, are also important for host–guest binding.

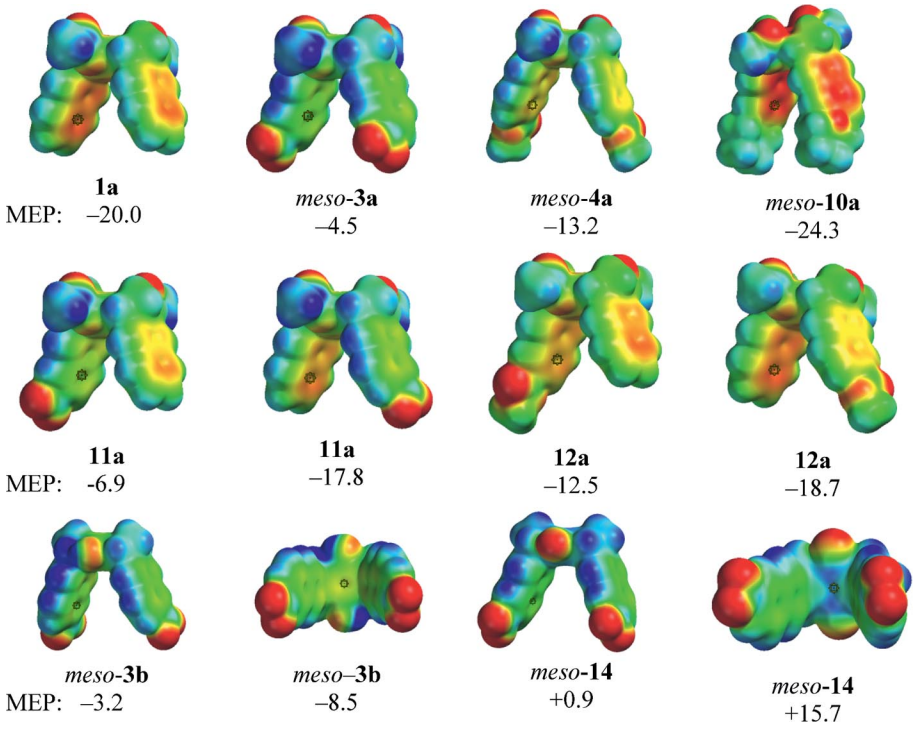


Figure 9. Electrostatic potential surfaces (EPS) of the substituted molecular clips (R^1 = OAc: R^2 = H, NO_2, CO_2CH_3, or NC_4H_4; R^1 = OH, R^2 = NO_2) and the dinitro-substituted quinone clip *meso*-**14** calculated by DFT using the structures optimized by AM1 (B3LYP/6-31G**//AM1).[16] The color code ranges from –25 kcal/mol (red) to +25 kcal/mol (blue). The listed molecular electrostatic potentials (MEPs in kcal/mol) were calculated at the marked positions.

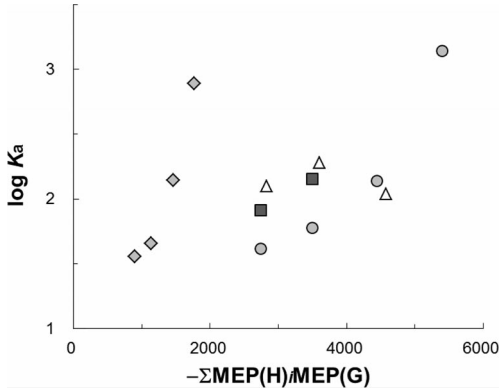


Figure 10. $\log K_a$ values plotted against $-\Sigma MEP(H)_iMEP(G)$ for complexation of TCNB (diamond) and KS (circle) with **1a**, **10a**, **11a**, and **12a** in $CDCl_3$ and of KS (square) and NMNA (triangle) with **1a**, **11a**, and/or **12a** in CD_3OD.

Conclusions

Dimethylene-bridged molecular clips bearing donor or acceptor groups at the naphthalene sidewalls and acetoxy, hydroxy, and methoxy groups at the central benzene spacer unit were synthesized as shown in Schemes 1, 2, 3, 4, and 5. The mixtures of the diastereomeric clips *meso*/*rac*-**2a**,**c**, -**3a**,**c**, -**4a**,**c** or -**5c** [prepared in one-pot reactions starting from the substituted tetrabromo-*o*-xylene derivative **15** (R^2 = Br, NO_2, CO_2CH_3, or $CONHCH_2CO_2CH_3$) and the bisdienophile **17a**,**c**] could be separated by HPLC or MPLC. The donor-substituted clips *meso*/*rac*-**10a**,**b**,**c** were prepared by palladium-catalyzed substitution of the bromide groups in *meso*/*rac*-**2c** by pyrrolidine, leading to *meso*/*rac*-**10c** and subsequent transformation of the methoxy groups of **10c** into hydroxy groups (**10b**) and finally into acetoxy groups (**10a**). The reaction of the "half-clip" **23** with tetrabromo-*o*-xylene derivative **15** (R^2 = NO_2 or CO_2CH_3) leads to the racemate of the molecular clips **11a** or **12a** (each monosubstituted at one naphthalene sidewall). In the case of the methoxycarbonyl-substituted clips **4a** and **12a**, the stereoisomers were separated by HPLC on a chiral column and the separated enantiomers of each compound were assigned on the basis of their CD spectra. The host–guest complex formation was studied by ^{1}H NMR titration experiments for the substituted molecular clips **3a**,**b**, **4a**,**b**, **10a**,**c**, **11a**,**b**, and **12a**,**b** as host molecules and TCNB, KS, and NMNA as guest molecules, and the results were compared with those of the parent clips **1a**, **1b**, and **1c**. The complexation-induced ^{1}H NMR shifts of the guest signals provide good evidence that in each complex the guest molecule is clipped between the naphthalene sidewalls of the host molecules by attractive aromatic π–π and CH–π interactions, as is also suggested by force-field calculations (Figure 8). This structural assignment of the complexes is further confirmed by the single-crystal structure of the KS complex of mono-nitro-substituted clip **11a** (Figure 7), which resembles the complex structure of the parent clip **1a** with KS. The good correlation between the clip EPS modulated by the donor or acceptor substituents and the host–guest complex stability confirms the assumption that, in chloroform solution, the host–guest binding (resulting from attractive aromatic π–π and CH–π interactions) is largely electrostatic in nature, whereas in methanol solution additional binding forces (for example solvophobic effects) contribute to the host–guest binding. The optically active molecular clips (+)-**4**, (–)-**4a** and (+)-**12a**, (–)-**12a** are a good starting point for future studies of chiral molecular recognition and organic catalysis.

Experimental Section

Synthesis of the New Molecular Clips: See Supporting Information.

General Experimental Details: IR spectra were recorded with a Bio-Rad FTS 135 spectrometer. UV/Vis spectra were recorded with a J+M Tidas FG Cosytec RS 422 spectrometer. ^{1}H NMR, ^{13}C NMR, DEPT, H,H-COSY, C,H-COSY, NOESY, HMQC, HMBC, and ^{1}H NMR titration experiments were recorded with Bruker AMX 300 and DRX 500 spectrometers. Residual undeuterated solvent was used as an internal standard. The ^{1}H and ^{13}C NMR signals were assigned by the 2D experiments mentioned above. Positions of the protons of the methano bridges are indicated by the letters *i* (*inside*, towards the center of the molecule) and *a* (*outside*, away from the center of the molecule). MS were recorded with a Fison Instruments VG ProSpec 3000 (70 eV). All melting points are uncorrected. Column chromatography (liquid chromatography) was conducted with Florisil (Rotichrom, 60–100 mesh, Roth) or silica gel (0.063–0.2 mm). Preparative MPLC were conducted with a SL12S21 250/25 Column, with silica gel from KronLab. All solvents were distilled prior to use.

Determination of the Binding Constants, K_a, and the Complexation-Induced ^{1}H NMR Shift of the Guest Protons, $\Delta\delta_{max}$, by NMR Titration Experiments: The binding constants K_a and the complexation-induced ^{1}H NMR shifts of the guest protons $\Delta\delta_{max}$ were determined by NMR titration experiments. In each experiment the total guest concentration was kept constant and the total host concentration was varied, as described.[15]

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre. CCDC-864941 (for *meso*-**5c**) and -864942 (for *rac*-**11b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): DFT calculations of the electrostatic potential surfaces (EPS) of molecular clips, the procedures of the synthesis of the new molecular clips, determination of the binding constants, K_a, and the complexation-induced ^{1}H NMR shifts of the guest protons, $\Delta\delta_{max}$, by ^{1}H NMR titration experiments, UV/Vis spectra of clips **1a**, **1b**, and **1*** (R^1 = OAc, OH; R^2 = H), TCNB, and the host–guest complexes between TCNB and these clips, and the crystal structure data of *meso*-**5c** and host–guest complex KS·*rac*-**11a**.

Acknowledgments

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Kaufmann (University of Bonn, Germany) for assistance with HPLC separation of *meso*-**4a**, (+)-**4a**, (–)-**4a**, and (+)-**12a**, (–)-**12a** and for recording the CD spectra of the optically active stereoisomers. Y. I. thanks the Alexander von Humboldt Stiftung for generous support for his stay in Germany.

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[14] The calculation of the complex structures was performed with force field MMFF94 implemented in Spartan'04, Wavefunction, Inc., Irvine, CA, USA.

[15] The ^{1}H NMR spectrum of complex TCNB·**1a** in $CDCl_3$ does not show any broadening or splitting of the signal assigned to the guest protons by cooling the sample from room temperature to –60 °C, in contrast to the ^{1}H NMR signal assigned to the TCNB protons in the complexes of the trimethylene-bridged clip and the diacetoxynaphthalene tweezer (R = OAc, Figure 1). M. Lobert, H. Bandmann, U. Burkert, U. P. Büchele, V. Podsadlowski, F.-G. Klärner, *Chem. Eur. J.* **2006**, *12*, 1629–1641.

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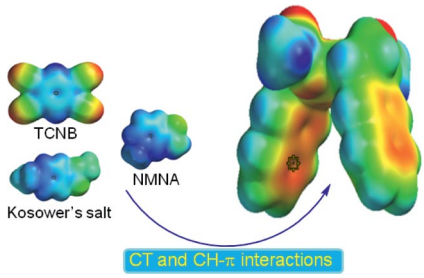
Host–Guest Systems

New donor/acceptor-substituted chiral molecular clips form host–guest complexes with 1,2,4,5-tetracyanobenzene (TCNB), *N*-methyl-*p*-(methoxycarbonyl)pyridinium iodide (Kosower's salt), and *N*-methylnicotinamide iodide (NMNA) through charge-transfer and CH–π interactions.



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Donor/Acceptor-Substituted Chiral Molecular Clips – Synthesis and Host–Guest Complex Formation

Keywords: Donor-acceptor systems / Electrostatic interactions / Host-guest systems / Charge transfer / Pi interactions

