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 bistilenophiles (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 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-methyl nicotinamide 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 substrate, 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 supramolecular structures 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 cycloextrins,9 cyclophanes,10–12 carcerands,13 cryptophanes,14 cucurbit[n]urils (CB[n]),15 and supramolecular capsules16 (formed by self-assembly of suitable molecular building blocks), noncyclic compounds with cavities of flexible size, which are frequently termed as molecular tweezers17 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 (π–π, CH–π, and cation–π 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 benzene20 or in the protein structures mentioned above, can be explained with a simple electrostatic model for benzene consisting of a positively charged π 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-diaryl naphthalene 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, where he is presently 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.
mutant cycle by replacing one of the terminal substituted benzene rings after the other with alkyl groups in the bimolecular complex 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 π–π and CH–π interactions. Here the question can be addressed of whether the magnitude of the complex stabilization is dependent on the orientation 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

\[
\begin{align*}
R^1 & : H \quad OAc \quad OH \quad OMe \quad OCH_3CO_{Et} \quad OCH_2CO_2 \quad OP(CH_2)O \quad N(n-Bu)_2 \\
R^2 & : H \quad OAc \quad OH \quad OMe \quad OCH_3CO_{Et} \quad OCH_2CO_2 \quad OP(CH_2)O \quad N(n-Bu)_2 \\
(a) & : \quad \text{b} \quad \text{c} \quad \text{d} \quad \text{e} \quad \text{f} \quad \text{g} \\
R^1 & : OAc \quad OAc \quad OH \quad OMe \\
R^2 & : OH \quad OCH_3CO_{Et} \quad OCH_2CO_2 \quad O(CH_2)_2CH=CH_2 \\
(h) & : \quad \text{i} \quad \text{j} \quad \text{k}
\end{align*}
\]

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

\[
\begin{align*}
R^1 & : \quad \text{R}^2 \\
(8, n=0) & \quad (9, n=1) \\
(10, n=0) & \quad (13, n=1) \\
\text{2} & \quad \text{10} \\
\text{11, n=0} & \quad \text{12, n=1} \\
\Delta T & \quad \text{16, n=0} \quad \text{16, n=1} \\
\text{DDQ} & \quad \text{3, n=0} \quad \text{4, n=1}
\end{align*}
\]
Alder reactions, proceeding with a high degree of stereo-
interaction between donor (D) and acceptor (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 acetylene 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 1H 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 1H 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, Δδmax, of the substrate protons, the association constants, K, and, hence, the Gibbs enthalpies of association, ΔG, were determined by 1H 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.

Table 1. Maximum Complexation-Induced 1H NMR Shifts of the Substrate Protons, Δδmax = δ0 – δcomplex, Association Constants, K, (M–1), and Gibbs Enthalpy, ΔG (kcal/mol), for the Formation of Host–Guest Complexes in CDCl3 at 21 °C (1a, 2a) and 25 °C (4), Respectively

<table>
<thead>
<tr>
<th>substrate</th>
<th>K</th>
<th>ΔG</th>
<th>Δδmax</th>
<th>K</th>
<th>ΔG</th>
<th>Δδmax</th>
<th>K</th>
<th>ΔG</th>
<th>Δδmax</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-DCNB 21</td>
<td>10</td>
<td>-1.3</td>
<td>3.5</td>
<td>(a) Neutral</td>
<td>110</td>
<td>-2.8</td>
<td>4.3</td>
<td>44</td>
<td>-2.2</td>
</tr>
<tr>
<td>m-DCNB 22</td>
<td>85</td>
<td>-2.6</td>
<td>5.3 (H+)</td>
<td>40</td>
<td>-2.1</td>
<td>5.2 (H+)</td>
<td>11</td>
<td>-1.4</td>
<td>3.1 (H+)</td>
</tr>
<tr>
<td>o-DCNB 23</td>
<td>&gt;10b</td>
<td>&lt;6.7</td>
<td>5.9</td>
<td>35</td>
<td>-2.1</td>
<td>1.6</td>
<td>&gt;10b</td>
<td>&lt;6.7</td>
<td>4.7</td>
</tr>
<tr>
<td>TCNB 24</td>
<td>17</td>
<td>-1.7</td>
<td>3.5</td>
<td>45</td>
<td>-2.2</td>
<td>5.5</td>
<td>63</td>
<td>-2.4</td>
<td>3.0</td>
</tr>
<tr>
<td>TA 25</td>
<td>1100</td>
<td>-4.8</td>
<td>2.9</td>
<td>8</td>
<td>-1.2</td>
<td>1.3</td>
<td>20</td>
<td>-1.8</td>
<td>2.8</td>
</tr>
<tr>
<td>p-DNB 26</td>
<td>26</td>
<td>-1.6</td>
<td>1.2</td>
<td>11</td>
<td>-1.2</td>
<td>3.6</td>
<td>2600</td>
<td>-4.6</td>
<td>3.3</td>
</tr>
<tr>
<td>FDNB 27</td>
<td>3500</td>
<td>-4.8</td>
<td>1.5 (H+)</td>
<td>30</td>
<td>-2.1</td>
<td>4.5</td>
<td>36</td>
<td>-2.1</td>
<td>4.5</td>
</tr>
<tr>
<td>TFb 28</td>
<td>35b</td>
<td>-2.4</td>
<td>1.6 (H+)</td>
<td>30</td>
<td>-2.0</td>
<td>3.2 (α-H)</td>
<td>37</td>
<td>11</td>
<td>-1.9</td>
</tr>
<tr>
<td>Pyr 30</td>
<td>56</td>
<td>-2.4</td>
<td>1.5 (H+)</td>
<td>4400x,d</td>
<td>&lt;5.0</td>
<td>4.6</td>
<td>2600x,d</td>
<td>&lt;4.7</td>
<td>2.9</td>
</tr>
<tr>
<td>p-BQ 31</td>
<td>130c</td>
<td>-2.9</td>
<td>1.6 (H+)</td>
<td></td>
<td></td>
<td></td>
<td>990</td>
<td>-4.0</td>
<td>0.7 (H+)</td>
</tr>
<tr>
<td>TCNQ 32</td>
<td>25c</td>
<td>-1.9</td>
<td>2.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH2CN</td>
<td>30</td>
<td>-2.0</td>
<td>3.2 (α-H)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* In CDCl3/acetone-d6 (1.2). b In CDCl3/acetone-d6 (1.1). c In acetone. d Determined with 2b as receptor.

Table 2. Δδmax, K (M–1), and ΔG (kcal mol–1) for the Formation of Host–Guest Complexes in CDCl3 at 25 °C

<table>
<thead>
<tr>
<th>substrate</th>
<th>receptor 5c</th>
<th>receptor 7c</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCNB 24</td>
<td>2180</td>
<td>-4.6</td>
</tr>
<tr>
<td>p-DNB</td>
<td>16</td>
<td>-1.6</td>
</tr>
<tr>
<td>FDNB 27</td>
<td>246</td>
<td>-3.3</td>
</tr>
<tr>
<td>TNF 28</td>
<td>45</td>
<td>-2.3</td>
</tr>
<tr>
<td>TCNQ 32</td>
<td>137</td>
<td>-2.9</td>
</tr>
<tr>
<td>Kosower salt 33</td>
<td>1080</td>
<td>-4.1</td>
</tr>
<tr>
<td>MePyr 34</td>
<td>3500</td>
<td>-4.8</td>
</tr>
<tr>
<td>MeVio 35a</td>
<td>56b</td>
<td>-2.4</td>
</tr>
<tr>
<td>DeVio 35b</td>
<td>130c</td>
<td>-2.9</td>
</tr>
<tr>
<td>BzVio 35c</td>
<td>4400x,d</td>
<td>&lt;5.0</td>
</tr>
<tr>
<td>TrpBF3 36</td>
<td>25c</td>
<td>-1.9</td>
</tr>
<tr>
<td>n-Bu2NHBF3 37</td>
<td>30</td>
<td>-2.0</td>
</tr>
</tbody>
</table>

* Measured in CDCl3/acetone-d6 1:1.

Table 3. Enthalpies, ΔH (kcal mol–1), Entropies, ΔS (cal mol–1 K–1), and Volumes, ΔV (cm3 mol–1), of Association at 25 °C in CDCl3

<table>
<thead>
<tr>
<th>substrate</th>
<th>ΔH</th>
<th>ΔS</th>
<th>ΔV</th>
<th>ΔH</th>
<th>ΔS</th>
<th>ΔV</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-DCNB 21</td>
<td>-2.6</td>
<td>+0.5</td>
<td>+1.5</td>
<td>-2.9</td>
<td>+7.6</td>
<td></td>
</tr>
<tr>
<td>p-DCNB 21a</td>
<td>-3.8</td>
<td>-3.1</td>
<td>-1.1</td>
<td>-3.8</td>
<td>-0.2</td>
<td>-1.1</td>
</tr>
<tr>
<td>TA 25</td>
<td>-6.0</td>
<td>-14.1</td>
<td>+0.6</td>
<td>-2.2</td>
<td>-2.4</td>
<td></td>
</tr>
<tr>
<td>p-BQ 31</td>
<td>-6.5</td>
<td>-15.3</td>
<td>-3.0</td>
<td>-2.6</td>
<td>-3.8</td>
<td></td>
</tr>
</tbody>
</table>

* In benzene-d6.
Scheme 5. Synthesis of the Dimethylene-Bridged Clips 5–7

\[ \begin{array}{c}
R & \text{Nal, DMF, 65°C, CaCO}_3, \text{100 mbar, 5h} \\
2 & \text{Br} \\
\end{array} \]

\[ \begin{array}{c}
R & \text{primary adducts} \\
2 & \text{Br} \\
\end{array} \]

\[ \begin{array}{c}
\text{Scheme 6. Survey of the Substrates Forming Complexes with 1–7 as Receptors}^a \\
\end{array} \]

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

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\[^a^\text{The complex formation may induce a conformational change in the receptor.}\]
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, $\Delta H$, entropy, $\Delta S$, and volume of association, $\Delta V$—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. 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 $+7.6 \text{ cal mol}^{-1} \text{ K}^{-1}$). The volumes of association show, however, only a small variation around the zero value ($\Delta V = -3.0$ to $+1.5 \text{ cm}^3\text{mol}^{-1}$). 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 $\Delta S$ while having only a small influence on $\Delta V$.

Complex Structures and Dynamics

The structures of several complexes could be determined by single-crystal structure analyses. According to the
structures shown in Figures 1 and 2, 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 1f surprisingly form complexes with the cesium cation Cs+. The formation of (Cs+)2@1f can be detected in its 1H NMR spectrum in CD3OD by the downfield shift of the OCH2COO− signal (Δδ = −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. 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.

According to force-field calculations, 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,
Molecular Tweezers and Clips as Synthetic Receptors

The interaction of the TCNB molecule between two DNN molecules, in the crystalline state, the complex shows an optimal 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 complexion-induced $^1$H NMR shifts, $\Delta \delta_{\text{max}}$, 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). 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. In the $^1$H NMR spectrum of p-DCNB 21a@2a in solution, only one signal at $\delta = 3.5$ is observed for $H^a$ and $H^b$, even at low temperature ($\sim 70 \, ^\circ C$), 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 $-70 \, ^\circ C$). 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 $137 \, ^\circ C$. 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 21a@2a. However, if a larger fragment of the solid-state structure is considered (Figure 6), it becomes clear that the 60° “flip” would move the CN groups of the substrate in the transition state too close to

<table>
<thead>
<tr>
<th>$^1$H NMR</th>
<th>CHCl$_3$</th>
<th>solid-state</th>
<th>computed$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$H^a$</td>
<td>3.4 (4.3)</td>
<td>5.6 (2.2)</td>
<td>5.8 (2.7)</td>
</tr>
<tr>
<td>$H^b$</td>
<td>3.5 (4.3)</td>
<td>2.0 (5.6)</td>
<td>1.7 (6.3)</td>
</tr>
</tbody>
</table>

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. In the $^1$H NMR spectrum of p-DCNB 21a@2a in solution, only one signal at $\delta = 3.5$ is observed for $H^a$ and $H^b$, even at low temperature ($\sim 70 \, ^\circ C$), 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 $-70 \, ^\circ C$). 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 $137 \, ^\circ C$. 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 21a@2a. However, if a larger fragment of the solid-state structure is considered (Figure 6), it becomes clear that the 60° “flip” would move the CN groups of the substrate in the transition state too close to

![Figure 5](image-url)
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 \(180^\circ\) “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, \(\lambda_{\text{max}} = 420\) nm), showing a complexation-induced \(^1\text{H} NMR shift of the TCNB protons by \(\Delta\lambda_{\text{max}} = 5.9\) in solution, which is of comparable size to the \(\Delta\lambda_{\text{max}}\) value of H^b in the solid-state \(^1\text{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\text{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 \(\Delta G^f = 11.7\) 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 7 and 8). In the \(^1\text{H} NMR spectra of 2:1 mixtures of receptors such as 2a,b and 4 and substrates

\[25^\circ\text{C}: \Delta \lambda(H^a, H^b) = 2.8 \text{ (fast exchange)}\]
\[-55^\circ\text{C}: \Delta \lambda(H^a, H^b) = 2.4, 3.0 \text{ (slow exchange)}\]
\[\Delta G^f = 11.7 \text{ kcal/mol}\]

\[-18^\circ\text{C}: \Delta \lambda(H^a, H^b) = 3.5 \text{ (fast exchange)}\]
\[-105^\circ\text{C}: \Delta \lambda(H^a, H^b) = 2.9, 4.4 \text{ (slow exchange)}\]
\[\Delta G^f = 8.2 \text{ kcal/mol}\]

**FIGURE 7.** Temperature-dependent \(^1\text{H} NMR spectra of (a) 24@2b and (b) 24@4 in toluene-\(d_8\).
such as TCNB 24 and TrpBF₄ 36, which form stable complexes, separate signals of the 1:1 complexes and the excess of free receptors are observed at low temperatures²⁴,²⁶,³².

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 line-shape 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, \( \Delta G \) = 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.

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

**FIGURE 9.** Activation parameters \( \Delta H \) (kcal/mol), \( \Delta S \) (cal mol⁻¹ K⁻¹), and \( \Delta G \) (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 ¹H NMR spectra of 2:1 mixtures of 2a and 24 in (CDCl₂), 2b and 36 (in CDCl₃/CD₃OD (1:1)), and 4 and 24 (in toluene-d₈).²⁴,²⁶,³²
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).

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 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 ($\Delta H_R$) (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$_3$CN, 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).

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. 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 $^1$H NMR spectrum of NAD$^+@5g$ and that the $\Delta \delta_{\text{max}}$ 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.

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

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

a) Broad signals in $^1$H-NMR spectrum of 5g and 38 in D$_2$O.

b) Precipitation of the complex after mixing 40 and 5g in CD$_3$OD.
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...
substances 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 substrate10 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 substances in aqueous solution. The synthesis of such derivatives is in progress.

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