Direct Assignment of Enantiofacial Discrimination on Single Heterocyclic Substrates by Self-induced CD

Carsten Siering,[b] Stefan Grimme,[b] and Siegfried R. Waldvogel*[a, b]

Abstract: The first direct assignment of highly dynamic enantiofacial discrimination acting on a single heterocyclic substrate has been achieved by a combination of experimental and theoretical CD spectroscopy. The interaction of chirally modified hosts based on triphenylene ketals with appropriate prochiral guests can lead to the preferential formation of one diastereomeric host–guest complex. This reversible stereoselective binding transmits the chiral information from remote chiral groups in the host to the strongly absorbing triphenylene chromophore, which gives rise to self-induced CD. This effect was exploited for the determination of the enantiofacial recognition in various host–guest systems. Inversion of the steric demand either of the chiral substituents at the host or of the prochiral guest leads to almost complete inversion of the resulting CD spectra. For the assignment of the absolute stereochemistry of the complexes, a combined molecular dynamics/quantum-chemical approach was successfully employed. Despite the size and the highly dynamic character of the supramolecular systems, fundamental properties of the systems and details of the spectra were simulated accurately, providing access to fast and reliable assignment of the enantiofacial preference. The results are highly consistent with available X-ray data.

Keywords: CD spectroscopy · chirality · host–guest systems · receptors · supramolecular chemistry

Introduction

When Thomson, later Lord Kelvin, introduced the term "chirality" in 1884, he made use of the most prominent pair of enantiomers in our life: our hands.[1] It seems trivial to mention which face of a hand we are looking at on the basis of some structural features on the surface. But what if we didn't know about the nails and the knuckles on the upper side? What if we had only the two-dimensional, prochiral representation? One could use a chiral mold as shown in Figure 1, in which only one face of the hand will fit. With the knowledge of which hand is used, one can assign the faces unequivocally. As depicted, it is possible to address each face of each hand with these molds, to describe "receptors" that distinguish between the faces of a "guest".

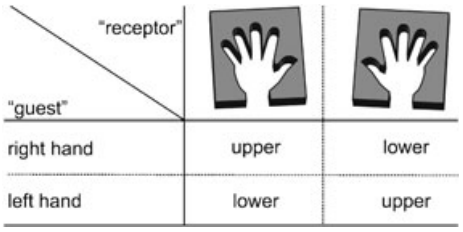

Figure 1. Model for a chiral receptor and a prochiral guest. To match the mold, one has to put the upper face of the right hand into the left mold and the lower face into the right one.

The guests presented in this report are substituted oxopurines, which share some structural properties with a "two-dimensional" hand in the terms described above. They are prochiral and thus have two faces (α/β),[2] and they have some substituents representing the fingers. Is there also a molecular mold for these compounds, a way to address one of the two faces of the whole prochiral molecule? Are there "left hand" and "right hand" guests that bind with the opposite face to the same receptor?

For aromatic compounds it has so far only been possible to solve the first challenge by use of covalently bound metal

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fragments such as $Cr(CO)_3$ and resolution of the resulting racemate.[3] Therefore, it is highly desirable to develop new methods for reversible enantiofacial discrimination of prochiral (hetero)aromatic compounds. Further development of these concepts will allow the selective blocking of one enantiotopic face and directly yield the desired product in an enantioselective fashion. The appropriate tools to meet this challenge are provided by supramolecular chemistry.

Exploiting the strongly directed nature of hydrogen bonding leads to supramolecular aggregates in a highly controlled fashion.[4] Supramolecular chemistry, however, has gone far beyond molecular recognition: the transfer of chiral information into these aggregates has meanwhile been established[5–7] and enantioselective recognition is a field of major interest. Over the past decades, many approaches have been reported involving chiral macrocyclic receptors,[8] cyclodextrins,[9] and other systems,[10] as well as supramolecular systems such as capsules[11] and rosettes,[12] that are capable of differentiating between enantiomeric guests. The binding is often based on electrostatic interactions, while only a few cases involve the binding of a neutral guest.[13] Before our initial reports there was no supramolecular approach for enantiofacial discrimination on a prochiral aromatic compound as a whole.[14]

Modified triphenylene ketals (**1**; Figure 2) are capable of binding compounds that feature hydrogen bonding acceptors

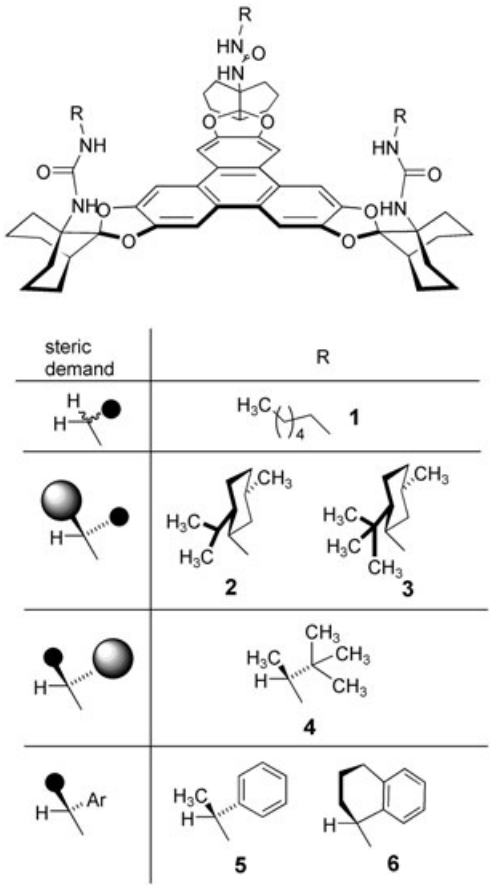

Figure 2. Derivatives of triphenylene-based receptor molecules.

in a planar C_3- or *pseudo*-C_3 symmetric pattern. Caffeine (**7**) binds to **1** with high affinity inside the receptor to form a defined 1:1 complex (Figure 3).[15] The prochiral guest is positioned in a coplanar fashion relative to the triphenylene

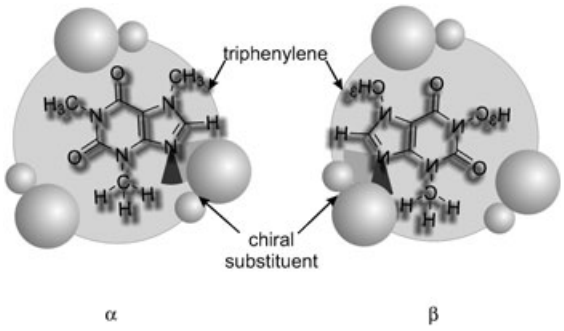

Figure 3. Diastereomeric complexes formed by aggregation of caffeine with a receptor based on triphenylene ketals. The stereodescriptor denotes the face of the caffeine pointing towards the triphenylene moiety.

platform, giving rise to planar chirality. Thus, a pair of enantiomeric complexes is obtained. Application of a chiral host results in two diastereomeric aggregates, allowing the detection of both species by physical means. A chiral environment close to the hydrogen bonding sites should maximize the face-specific interactions that allow enantiofacial selectivity.

One structural property closely related to the face of the guest is the sense of decrease of steric demand ("steric decrease") close to the hydrogen bond acceptors of the guests, as indicated in Figure 4. For caffeine (**7**), the environment of

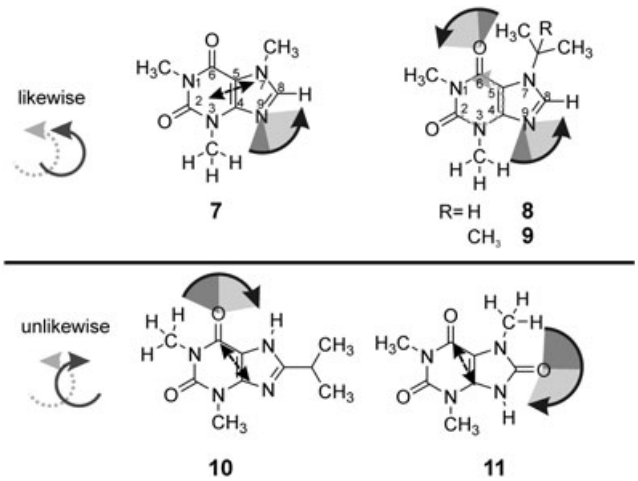

Figure 4. Collection of alkylated oxopurines used for the investigations. In order to illustrate the steric bulk close to the most asymmetric binding sites schematically, the adjacent substituents were expanded. The dashed, gray arrows follow the systematic numbering (and indicate that the β face is shown), while the black arrows indicate the sense of rotation on going from the more to the less hindered side of the hydrogen bonding acceptor; the double arrows indicate the orientation of the electric transition dipole moment of the lowest π–π* transition at 270–280 nm (TD-PPP, single structure; see Theoretical Section for details).

the each of the oxo functions is fairly mirror symmetric, and no such assignment of a "gradient" is applicable. However, the imidazolo nitrogen atom (N9) is buried in a strongly dissymmetric pocket, since the N3 methyl substituent occupies more space than the hydrogen at C8. It is necessary to modify the receptor in such a way that the steric requirements are only complementary for one face. As indicated in Figure 3, this is achieved by installing homochiral substituents with very different steric demands close to the binding site.

The first examples (**2**–**6**) of such optically pure host molecules have α chiral substituents at their urea moieties.[14] The influence of their stereochemical information on the complexes could be shown by X-ray crystal analysis and low-temperature NMR experiments. However, the caffeine complexes have proven to be highly dynamic, which impeded the assignment of absolute stereochemistry in solution by NOE experiments.

The most promising tool to elucidate the preferential orientation in solution is CD spectroscopy.[16,17] Investigation of structure and dynamics in supramolecular assemblies often makes use of induced CD (ICD).[18] This effect occurs when a chiral, UV-inactive molecule interacts with an achiral compound bearing a chromophore. While neither will exhibit any CD signal as a sole component, their complex may reveal significant Cotton effects. This can be due either to coupling of the transition moments ("exciton coupling")[19] or to chiral structural perturbations. The plethora of investigations into cyclodextrin inclusion compounds is mainly based on the latter effect.[20] Harata's and Kodaka's rules are prominent examples for correlation of supramolecular structures with CD spectra.[21] There are also several examples in which the association of a chiral, non-UV active compound to a peripheral binding site induces structural changes in a large supramolecular assembly,[6] even allowing racemic mixtures to be transformed into their enantiomerically pure forms.[7] If several chromophores are arranged in these cases in a nonracemic, chiral manner, the resulting exciton coupling is the origin of the Cotton effect.

The systems described here combine those concepts. As in the case of cyclodextrins, 1:1 complexes are obtained exclusively. The remote (but covalently linked) chiral units control the structure of the aggregate and through that the CD. The major part of the CD intensity is supplied by the exciton coupling between the two chromophores of host and guest. In this specific case the host contributes the two pivotal elements for induced CD—a strong chromophore and the chiral information—while the guest just "connects" these two. Consequently, we will refer to this effect as self-induced CD (SICD).

The interpretation of CD spectra in terms of molecular structures can be established by quantum chemical (QC) methods.[22] It is common to use single structures for such calculations. There are a few reports involving combinations of classical molecular dynamics (MD) with QC techniques to obtain averaged theoretical spectra that agree better with experimental results for flexible systems. So far, all studies have been limited to chromophores covalently linked to the chiral moieties.[23,24] Here we report the first application of such a combined MD/QC approach to non-covalently bound supramolecular systems.

This report is organized as follows: the first part deals with CD experiments, whereas the second part first describes the development of the methodology for the calculations and afterwards gives the specific results for the investigated systems.

Results and Discussion

CD spectroscopy

Investigated systems: All the investigated guest molecules have the purine backbone in common and exhibit three hydrogen-bond acceptors complementary to the urea moieties in the receptor. Because of the different substitution patterns, however, there are some structural differences. One criterion for classification of these guests is the sense of "steric decrease", as introduced before for caffeine (**7**). Two classes of guests are identified: either the sense is the same as is given by the systematic numbering of the ring system ("likewise") or it is the opposite ("unlikewise").[25] Here, we can revisit the analogy to the hands: looking at the same face of both hands, we observe opposite rotation when going from the thumb to the little finger. Thus, the relation between "likewise" and "unlikewise" guests is equivalent to that of the two-dimensional pair of hands.

The structural features of caffeine (**7**) were discussed in Figure 3. The achiral system **1** had been designed and developed to bind this compound and its association with this guest was already well known.[15] Therefore, we used this particular compound as starting point for our investigations. The existence of pronounced dissymmetry at more than one binding site should enhance the selectivity. For that reason, compounds **8** and **9** (Figure 4), containing either an isopropyl (**8**) or a *tert*-butyl (**9**) moiety at N7, were synthesized starting from theophylline. 1,3,7-Trimethyluric acid (**11**) belongs to the "unlikewise" class of guest molecules (Figure 4). NMR experiments indicated an extremely high affinity—of $>200\,000\,\mathrm{M}^{-1}$ ($CDCl_3$)—for the receptor. This compound is bigger than the other guests and features a slightly altered geometry of the hydrogen bonding pattern, since N9 no longer serves as hydrogen bond acceptor. Instead, the C8 carbonyl, which is positioned at a very exposed position, will interact with the urea moieties. In addition, the theophylline derivative (**10**) was prepared and investigated.[26] As depicted in Figure 4, N9 is hidden between two bulky alkyl substituents, whereas the carbonyl at C6 is exposed to a highly asymmetric environment with a decreasing steric demand in the "unlikewise" manner.[26,27]

The synthesis of the receptors was accomplished by addition of optically pure isocyanates to a triphenylene-based trisamine.[14,28] This procedure yielded compounds **2**–**6** (Figure 2) with known absolute configurations. The menthyl

derivatives **2** and **3** protrude more deeply into the cavity than the *tert*-butyl-substituted **4**, which should enhance the selectivity. In addition to this, the sense of the steric demand is inverse for **2**, **3**, and **4** as indicated in Figure 2. Host **5** is a particular case, as the phenyl substituents can freely rotate and consequently represent substituents of less predictable size. A closely related compound is **6**, though lacking the rotational freedom in the phenyl moieties.

General considerations: Acetonitrile and dichloromethane are the only solvents with sufficient transparency in the wavelength range of 230–350 nm that are capable of dissolving both receptors and guests. In dichloromethane, significant changes in the CD spectra were observed upon addition of the guests, whereas the same procedure in acetonitrile did not yield any effect, indicating that acetonitrile strongly interferes with the complex formation. In accordance with the results from NMR and X-ray analysis, this underlines the supramolecular, hydrogen-bonding nature of the host–guest system. Dichloromethane was therefore used as solvent despite its inferior optical properties at lower wavelengths.

The triphenylene moiety in the host is the strongest chromophore in all investigated systems. As shown in Figure 5, the UV spectrum reveals an ε_{max} at 283 nm more than ten times higher than the ε_{max} of caffeine at about 270 nm.

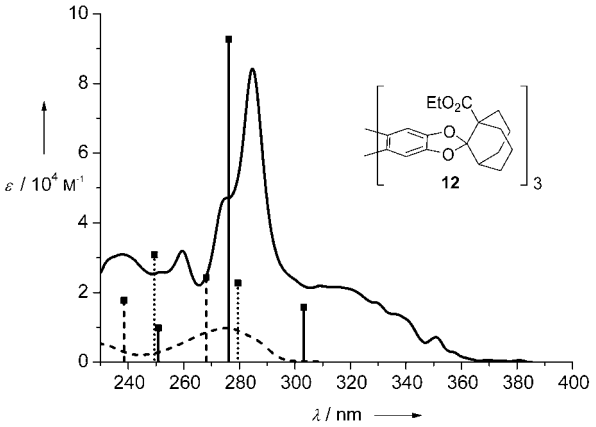

Figure 5. Experimentally measured UV spectra of triphenylene ketal triester **12** (——)[15] and caffeine (**7**; -----); calculated intensities (single structure, TD-PPP, vide infra) of **12** (——),[15] **7** (-----), and 1,3,7-trimethyluric acid (**11**) (•••••).

CD spectra: The CD intensities of the aliphatic hosts **2**–**4** in the absence of guest molecules are close to zero (i.e., $\Delta\varepsilon < 2\,\text{M}^{-1}\text{cm}^{-1}$). This was anticipated, since the chiral moieties are located more than 5 Å above the triphenylene chromophore and negligible chiral distortion of the triphenylene moiety should occur.

Titration of compound **4** with caffeine (**7**) yielded a significantly modified spectrum with a well defined change of sign at 260 nm (see Figure 6). When the same experiments were performed on the (1*R*,3*R*,4*S*)-menthyl-substituted systems **2** and **3**, inverted behavior with significantly increased intensity and slightly altered curve shape was detected. However, the intercepts with the abscissa occurred at the very same wavelengths.

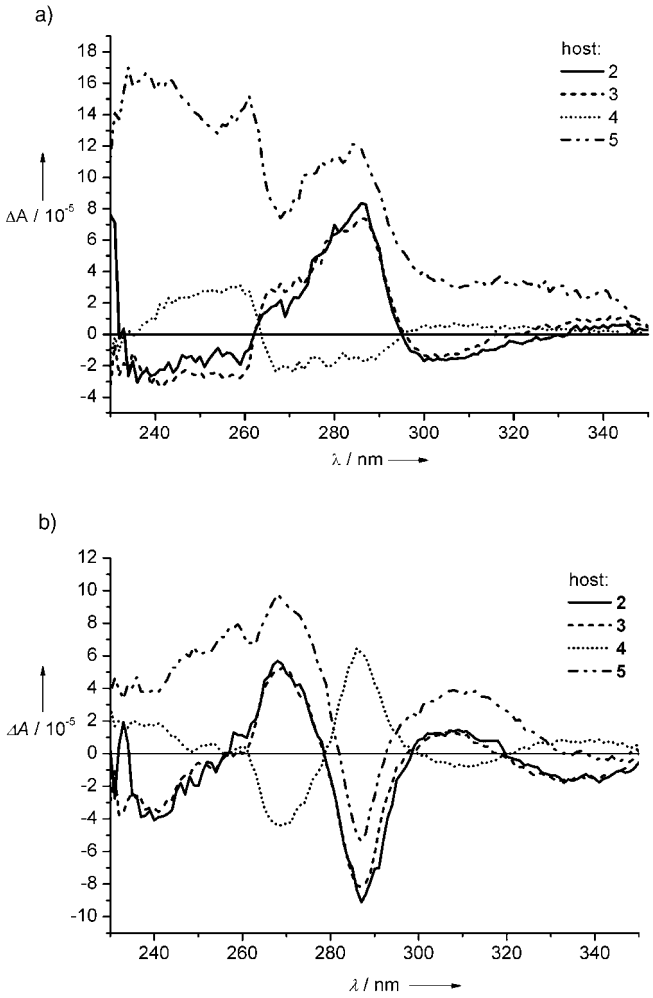

Figure 6. CD spectra of caffeine (**7**) (a) and 1,3,7-trimethyluric acid **11** (b) with menthyl-derived hosts **2** and **3**, *t*Bu-ethyl substituted **4**, and phenylethyl derivative **5**; c(host) = 1×10^{-5} M, c(caffeine) = 1×10^{-4} M, c(trimethyluric acid) = 2×10^{-5} M, CH_2Cl_2.

The strong similarity (except for the inverted signs) between the CD spectra of the same guest with hosts of inverted steric demand implies that the CD-relevant interaction of the two can be regarded as enantiomorphous. This can only be the case if the chiral substituents in the host do not interfere with the generation of the Cotton effect, since this would render a pair of diastereomorphous excitations. Thus, the CD must mainly originate from the exciton coupling of the triphenylene with the guest chromophore, which is in full agreement with our initial assumptions. Since it is known from the X-ray crystal analyses that **4** prefers the opposite orientation of caffeine to **2** and **3**, these results indicate that the inversion of the spectra may be due to the changed enantiofacial preference.

Up to this point the relationship between the spectra of the two diastereomeric complexes (α/β) of one specific

host–guest pair is unclear, since they can not be experimentally obtained. If the chiral substituents only determine the ratio of both complexes, but allow the guest–triphenylene arrangement to form in a nearly enantiomeric fashion, almost inverse spectra should be obtained for the isolated aggregates.

1,3,7-Trimethyluric acid (**11**), which is almost insoluble in dichloromethane, dissolves instantaneously upon addition of a triphenylene ketal-based receptor. The spectra of the complexes obtained with this guest are generally smoother than of those with caffeine-related molecules (Figure 6). As to be expected from the higher affinity, saturation has already occurred after addition of two equivalents of the guest. The complexes of **11** with menthyl-substituted hosts **2** or **3** provide spectra with a positive band at 269 nm and a negative signal at 287 nm, while **4·11** again displays a completely inverted spectrum. The inversion of the signal upon changes of the steric demand at the receptor is apparently independent of the employed guest. However, caffeine and 1,3,7-trimethyluric acid yield opposite signs of the CD spectra near 290 nm when added to the same host. The cause of these findings may be differences in the electronic properties of the guests, in the face selectivity due to altered steric interactions, or in the geometry of the binding sites.

To exclude the last of these, the oxopurines **8** and **10** were used. These differ only in the position of one bulky substituent and therefore belong to the different classes of guests. The corresponding spectra are shown in Figure 7. The intensities of the CD bands are significantly lower than those of the caffeine complexes, indicating a reduced affinity towards the receptor due to the extended isopropyl substituent. However, addition of **8** or **10** to the same receptor gives rise to inverse signals in the range between 270–290 nm. These results underline that the local steric demand in the environment of the hydrogen bonding acceptors of the guest plays a pivotal role in the enantiofacial discrimination, while the different binding geometry does not seem to be the reason for this effect.

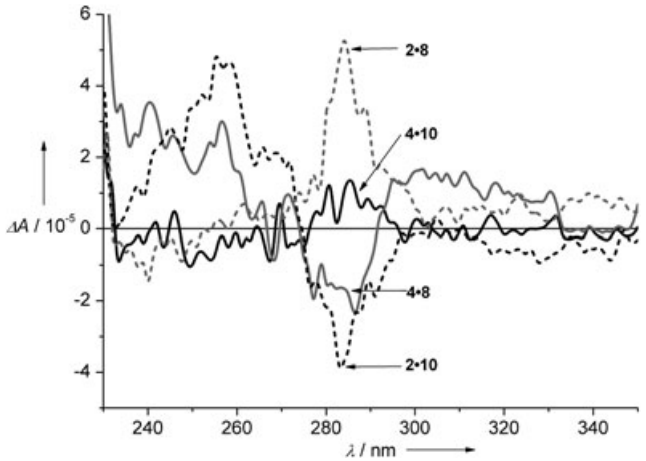

Figure 7. CD spectra of **10** (black) and **8** (gray) in **4** (——) and **2** (-----).

The aromatic substituents of receptors **5** and **6** complicate the situation, since they are involved in some exciton coupling with the triphenylene or the triphenylene–guest pair. Thus, the phenyl-substituted receptor **5** shows a comparably strong CD as a single compound, with two significant elements in the regions around 260 and 280 nm. Upon use of caffeine (**7**) or its derivatives **8** and **9** the 280 nm band experiences little change, whereas the low-wavelength signal grows significantly. As described above, 1,3,7-trimethyl uric acid (**11**) generally gives inverted spectra with respect to the caffeine data, but addition of this guest to **5** also results in a positive CD signal at 261 nm.[29] Consequently, the change of this signal is assigned to the general binding event rather than to a preferential orientation of the guest. The reorientation of the urea moieties and their chiral substituents upon binding is at this point the most viable explanation. This interpretation is further supported by the fact that in guest-free **6** with the fixed phenyl ring the signal at 260 nm shows a significantly elevated intensity relative to the signal at 290 nm than is the case in the system with the freely rotatable phenyl group. For **6·7**, smaller changes in this area are observed upon complex formation. If all receptor molecules are complexed by caffeine, the CD spectra of **5** and **6** are very similar, creating a consistent picture of the interactions between triphenylene and aromatic substituents. The CD spectra of these individual diastereomeric species will most probably not behave as mirror images since the phenyl–guest–triphenylene triad represents a diastereomeric arrangement. (see Theoretical Section for more details)

Affinities: Comparison of the signal intensities at the maxima between 280–285 nm revealed that the menthyl-derived systems **2** and **3** generally yielded more intense signals than the *t*Bu-ethyl-substituted receptor **4** (see Figure 8).

The binding constants for caffeine were determined for the different systems by CD titration experiments. The affinities for systems **2** and **4–6** are fairly comparable (see Table 1) and so are not the origin of the differences in the CD intensity. Apparently, the shape of the chiral substituent

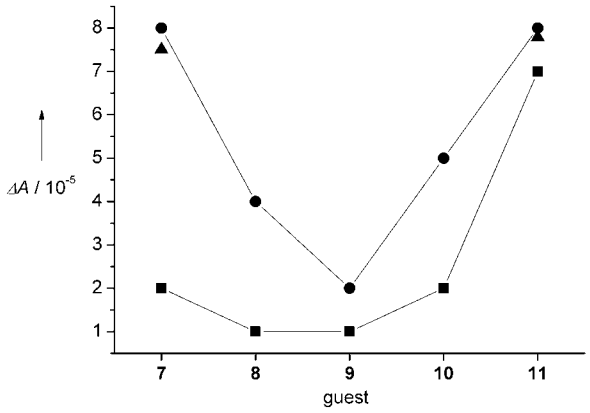

Figure 8. Absolute maximum signal intensities at 280–290 nm for complexes of menthyl-derived hosts **2** (●), **3** (▲), and *t*Bu-ethyl derivative **4** (■) with selected guests.

Table 1. Binding constants for various host and caffeine (**7**) as determined by CD spectroscopy.

Receptor	Binding constant [M^{-1}]
2	47000 ± 3000
4	45000 ± 11000
5	46000 ± 4000
6	56000 ± 8000

does not significantly influence the affinity for caffeine. The obtained binding constants are slightly higher than those derived from previous NMR experiments with the achiral receptor, yielding a value of $35600 \pm 2000\,M^{-1}$.[15] It is reasonable that the bulky substituents lead to even more greatly increased preorganization of the receptor and consequently to improved binding properties. This effect is further emphasized by the enlarged affinity found for the **6·7** system.

The decline of CD intensity on going from the menthyl-derived systems **2** and **3** to **4**, with the smaller *tert*-butyl substituent, might be explained in terms of different extents of enantiofacial discrimination. As discussed above, the diastereomeric complexes of a receptor are expected to exhibit inverse spectra. When a mixture of both aggregates is present in solution, partial cancellation will occur, leading to a spectrum of reduced intensity. Low-temperature NMR experiments showed that receptor **4** forms two caffeine complexes in solution, whereas the menthyl-derived **3** yields only a single diastereomeric aggregate.[14] This may imply that the CD intensity indeed correlates with the enantiofacial discrimination.

A synopsis of all spectroscopic measurements demonstrates that the shapes of the spectra below 280 nm are not uniform and are strongly dependent on the guest molecule. However, all spectra of the aliphatic receptors have in common that significant changes occur in the 280–290 nm range upon addition of guests. The changes in the intensity of this diagnostic band are tabulated for these complexes in Figure 9, which can be divided into four quadrants. The only exception is **4·9**. The specific reasons for this result are unknown, but deviations in the triphenylene–guest arrangement (i.e., distance, coplanarity) caused by the *tert*-butyl substituent may complicate this system.

Comparison of Figure 9 and Figure 1 reveals striking similarities. When the receptor (the mold) displays an inverted

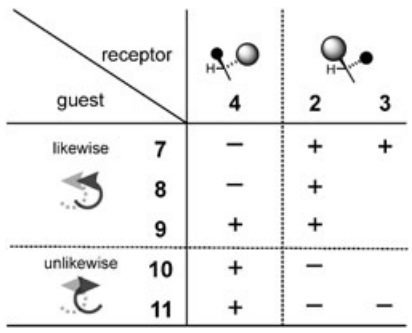

Figure 9. Signs of $\Delta A_{complex} - \Delta A_{empty}$ of various complexes at 283 nm.

steric demand, the guest (the hand) fits in with the other face than before. When likewise and unlikewise guests ("left and right hand") are used with the same receptor, they will both match, but with opposite faces.

In summary, we were able to demonstrate a close relationship between the steric demand of the chiral group, the orientation of the guest, and the ICD. Furthermore, we found indications that diastereomers formed upon association could display inverse CD spectra. To assign the absolute stereochemistry of the system, however, it is necessary to obtain corresponding reference data. Because of the rapid interconversion of the two complex species it is not experimentally possible to isolate either of the diastereomers. So this problem is addressed theoretically by calculation of the CD spectra of the different complexes and subsequent comparison with experimental data.

Outline of the simulations

Calculation of the spectra: As shown above, the contacts between the guest and the aliphatic substituents are of minor importance for the CD, whereas a strong dependency on the guest–triphenylene interaction is postulated. As all of the important electronic excitations of both host and guest involve π electrons, we decided to apply the Pariser–Parr–Pople (PPP) method in its time-dependent form (TD-PPP)[30] to calculate the spectral properties of the individual structures taken from classical MD trajectories. Each single-electronic transition was broadened with a Gaussian function with an initial half-band width of 0.04 eV. The resulting spectra obtained for the individual structures were averaged. The UV spectra were calculated in the same way in order to check the internal consistency of the procedure. Note that the parameters of the semiempirical PPP Hamiltonian have not been adjusted to reproduce data of these systems.

The technical setup of the calculations was tested by simulations of the CD spectra of conformationally rigid and nonrigid π systems. (*M*)-Helicene was used as reference in order to assert the quality of the calculated CD spectra. Reasonable agreement with experimental values in terms of wavelength accuracy and correctly located signs of the Cotton effects was observed for the obtained spectra. Simulation of benzene (2 ns, 200 structures, MD or MCSD (see below)) yields no significant CD ($\Delta\varepsilon_{max}/\varepsilon = 2\times10^{-6}$). Simulation of caffeine under similar conditions leads to a $\Delta\varepsilon_{max}/\varepsilon = 3\times10^{-5}$. The simulated effects obtained for the complexes under these conditions are significantly higher ($\Delta\varepsilon_{max}/\varepsilon > 1\times10^{-4}$).

Fortunately, both host and guest molecules are comparably rigid, which facilitates the calculation to some extent. However, because of the supramolecular nature of the complex and the size of the whole system, the orientation of the guest relative to the triphenylene is not very well defined. As is shown later, the CD is highly sensitive to small changes in the position of the guest, and for this reason classical energy minimization with a single-point spectral calculation was not suitable. Furthermore, this method is also not

appropriate for simulation of the structural diversity that should be present in solution at 300 K. We therefore decided to use molecular dynamics to generate a high number of representative structures, which were subsequently fed into the TD-PPP calculation in order to obtain the spectral data. A similar approach for covalently bound chromophores was recently reported by Bringmann et al.[23]

Selection and adaptation of the force field: Various force fields were tested for our system,[31] Schrodinger's MacroModel 7.1 package yielding the best results.[32] The best agreement with X-ray structure data was obtained with the AMBER* force field.[33] All calculations involving MacroModel were performed with an all-atom representation since the hydrogen atoms were required for automatic recognition of the π systems in the TD-PPP calculation.

For **4·7**, the original AMBER* force field yields structures that provide accurate predictions of the UV spectra in subsequent TD-PPP calculations. However, the lengths of equivalent bonds in the triphenylene unit differ significantly. The reason for these distortions is a substructure for 9,10-disubstituted anthracenes in the force field definition, which is wrongly attributed to the triphenylene. As an asymmetric triphenylene causes a strong CD by itself, the substructure was removed, resulting in significantly red-shifted UV and CD spectra.

Since the bond lengths in the triphenylene apparently have a strong impact on the spectra, we decided to modify the force field. As reference structures we used six sets of X-ray data from different triphenylene derivatives.[14,34] The bonds connecting the three "exterior" phenylene rings are significantly longer than a classical aromatic C–C bond. The all-benzoidal character of triphenylenes leads to reduced electron density at those bonds.[35] As this effect is not correctly addressed by a force field such as AMBER*, a new triphenylene substructure was introduced and the bond lengths were adjusted accordingly.

Initial simple energy minimizations of triphenylene revealed a significantly improved agreement with the X-ray data. A subsequent simulation of the complex **3·7** showed that the UV spectra were now also ameliorated. Test calculations using different force constants for stretch and bend interactions did not yield any significant improvements in the structural data.

To verify that the adaptations of the force field properly describe the triphenylene moiety, the UV spectrum of triphenylene was calculated and compared to experimentally measured values (Table 2).[36]

The excellent agreement between experimentally measured and calculated spectra demonstrates the quality of both the structural and the spectral calculations. The calculated line spectra of the triphenylene ketal and caffeine are given in Figure 5.

Simulation algorithm: All dynamics simulations were performed at a temperature of 300 K. The simulations were carried out with extended non-bonded cutoff distances of 20 Å for electrostatic and van der Waals interactions. For an approximate treatment of the solvent, Still's polarizable continuum model (GB/SA) was used with chloroform as solvent.[37] Integration times for the Newton equations were set to 1.0–1.5 fs. Simulation times were generally longer than 2 ns, with an equilibration time of at least 200 ps. If necessary, the hydrogen bonds were fixed at 2.3 Å during a 200 ps pre-equilibration phase in order to obtain stable complexes. Every 10 ps a structure was extracted from the trajectory for a subsequent TD-PPP calculation of a single spectrum. The convergence of the simulation was checked by the average energy and structural parameters such as the distance between guest and triphenylene as well as the intermolecular dihedral angle θ (see Figure 10).

Table 2. Comparison of calculated (TD-PPP) and experimentally obtained spectra of triphenylene.

Calcd λ [nm] (ε [M^{-1} cm^{-1}])	Exp[36] λ [nm] (ε [M^{-1} cm^{-1}])[a]
–	250 (90000)
257 (500000)	259 (180000)
270 (18000)	274 (20000)
284 (15000)	286 (20000)

[a] Solvent: cyclohexane

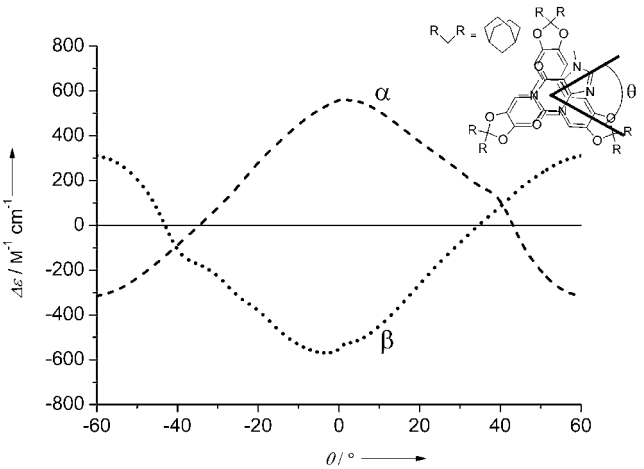

Figure 10. Calculated $\Delta\varepsilon_{max}$ at 284–290 nm depending on the rotation angle θ of caffeine arranged in coplanar fashion above the triphenylene for α (-----) and β (•••••) complex.

Great effort was put into the selection of the simulation method. We tested stochastic dynamics (SD), molecular dynamics, and a combined Monte Carlo/stochastic dynamics (MC/SD) approach.[38] The SHAKE algorithm was used for MD and SD to constrain the protons in order to accelerate the simulation.[39] SD simulations performed at constant temperature are supposed to deliver the physically most meaningful result since they simulate the canonical ensemble. A careful investigation of the resulting trajectories[40] revealed a periodic behavior pattern in the simulation, which appeared independently of the system size and shape, and so this approach was discarded. MD did not show these arti-

facts, but the convergence was poor. The last and most expensive method we tried was MCSD. For the MC variations we defined two torsions per receptor side chain and the caffeine position as degrees of freedom. This method gives the fastest convergence in terms of structure and energy: even starting from very different structures leads to the same results after a simulation time of 1.5 ns. However, since the Macromodel implementation of MCSD is not capable of working in conjunction with SHAKE, the calculation times are twice those of a normal MD.

The systems **4·7** and **3·7** were used for testing purposes since X-ray data are available for comparison. The simulated average distance between the planes spanned by the triphenylene and the guest is 3.30 ± 0.07 Å for the **4** complexes and 3.5 Å for the **3** complexes. The standard deviation of the individual simulations for this value, in the range from 0.2–0.3 Å, indicates that this geometrical parameter is highly conserved. The reference value taken from the crystal structures is 3.32 Å.

For the α and β complexes the signs of θ (see Figure 10) are inverted, while the absolute values of θ for the diastereomeric complexes are quite similar. For $|\theta|$ both receptor systems yield a mean value of $33 \pm 4°$.[41] The standard deviation in the individual calculations is quite small ($\pm 6°$). In the X-ray crystal structures the guest is slightly shifted and a higher value of 42° for the dihedral angle is observed.

The average structural parameters relating to the triphenylene and the guest exhibit good reproducibility by MCSD. More deviations are observed at the urea substituents, but since only the π systems of the complex are considered for the calculations of the CD spectra, this would not be expected to cause any problems.

The simulation algorithm used had no direct effect on the resulting CD spectra, it being found that comparable spectra were obtained when MCSD and MD were used. Since MCSD generally provides better and faster convergence in terms of energy and structural parameters, we discuss only spectra derived from these calculations.

Signal stability against parameter changes: The calculated CD signals below 280 nm are generally very sensitive to changes with regard to the receptor or the guest molecule and cannot be easily predicted. However, the sign of the diagnostic band at 280–300 nm correlates directly with the enantiofacial orientation of the guest molecule. A negative value is obtained for any β complex, whereas the α complexes always yield positive values. This is found even for poorly converged MD and SD simulations. Additionally, trajectories obtained from other force fields such as MM3 and MMFFs, which gave shifted spectra, correctly predict the sign of the main band. Apparently, the sign of the CD in this area is a very robust indicator of the enantiofacial preference.

Effects of sampling/line widths: To investigate their convergence, the mean CD spectra of several simulations were determined with different sampling rates. Just 50 structures are sufficient to predict the general pattern of the spectrum. However, in order to obtain reasonably converged spectra, it is necessary to use a minimum of 200 structures. We did not observe any pronounced line broadening with increased sampling rates, so we increased the "artificial" line broadening applied in calculation of the spectra from 0.04 eV to 0.2 eV in order to reproduce the observed band width of the experimental spectra. The calculated ε_{max} of the complex is at about $120000\,M^{-1}cm^{-1}$, which when compared to the experimental data is only too high by a factor of 1.3.

Results of the simulations

Empty receptors: Both as expected and as observed experimentally, the empty alkyl-substituted receptors do not show any significant CD ($\Delta\varepsilon_{max}$ (**4**) $\approx 1\,M^{-1}cm^{-1}$). Simulation of compound **6** yields a spectrum containing both significant elements of the experimentally measured spectrum at about 250 and 278 nm (see Figure 11, insert). Apparently, the sim-

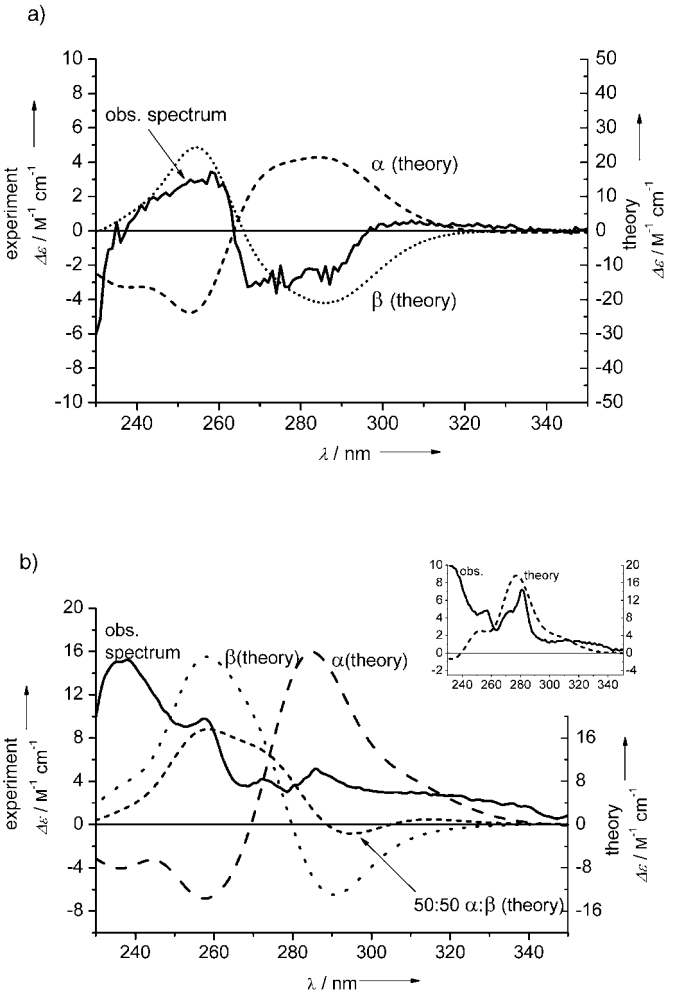

Figure 11. Comparison of experimental (——) and theoretical (α = – – –, β = – – – –) spectra; a) **4·7**; b) **6·7**, individual theoretical spectra for α and β complex (gray) and combined spectrum for α:β (black, – – – –); insert: calcd (– – – –) and experimental spectrum of the empty receptor.

ulation correctly reproduces the exciton coupling between these moieties.

Investigations of a static model system: To elucidate the influence of the position of the guest on the resulting CD, a simplified system consisting of a triphenylene ketal (without the urea parts) and caffeine was examined. It was assumed that the guest was situated at a distance of 3.3 Å in a coplanar fashion relative to the triphenylene and that the pyrimidine ring of the caffeine was centered above the platform. The CD was calculated for both the α and the β forms, as well as for various values of the intermolecular dihedral angle θ as shown in Figure 10.

The α and β complexes showed almost inverse values of $\Delta\varepsilon_{max}$ at 284–290 nm for any value of θ. Rotation of the guest above the triphenylene resulted in a tremendous variation of the signal intensity with a period of 120°. While the highest absolute values are obtained at 0° ($|\Delta\varepsilon| \approx 600$), inversion of the sign occurs in the range between 40° and 80° (see Figure 10; 80° corresponds to −40° due to the symmetry of the triphenylene) with a local extremum of $|\Delta\varepsilon| \approx 300$. The extreme overestimation of the CD intensities in relation to the experimentally measured values is caused by the use of a single minimized structure. Since the calculations described before gave absolute values for θ of about 30°, the relevant part of the plot is close to the intersection of the two curves. Therefore, it is essential to obtain detailed information on the position of the guest in order to avoid a wrong assignment.

As discussed before, the positions of the guests in the diastereomeric complexes are almost the same except for the different bound face and the sign of θ. Thus, in an equimolar mixture of both diastereomers, full cancellation of the signals should occur.

Caffeine complexes: The calculated spectrum of the system β-**4·7** in comparison with the experimentally measured data is shown in Figure 11. It shows negative signals in the area between 300 and 260 nm and positive signals in the area below 260 nm. Since the calculated spectrum of the corresponding α species is completely inverse, the experimentally observed spectrum can be unquestionably assigned to the β form. This is also supported by the average enthalpy obtained from the simulations, according to which the β structure should be slightly favored by 2.2 kJ mol^{-1}. Additionally, this result is consistent with crystallographic investigations of this complex, which rendered the β form exclusively.[14]

In a similar fashion, the calculated CD spectrum of α-**3·7** matches its experimentally measured counterpart, while the corresponding β complex gives rise to the inverse spectrum (see Supporting Information). In relation to the caffeine spectra, an additional signal is predicted at 270 nm, corresponding with the shoulder found experimentally.

1,3,7-Trimethyluric acid complexes: The calculated spectra of the complexes containing 1,3,7-trimethyluric acid (**11**) also give a bisignate sigmoidal curve shape. The shift of the abscissa intersection from 260 nm for caffeine complexes to higher wavelengths for 1,3,7-trimethyluric acid complexes could be reproduced by the calculation (see Supporting Information). However, the calculated position of the lower-wavelength signal is blue-shifted with respect to the experimental results. From these calculations it was possible to assign the experimentally determined spectra to β-**3·11** and to α-**4·11**, respectively.

Receptors with aromatic substituents: As discussed before, the aromatic substituents interfere with the rise of a CD signal as well, resulting in a complex interaction of triphenylene, guest, and chiral substituents. Hence, the formerly enantiomorphous arrangement of chromophores in the α and β complexes will now become diastereomorphous, so the calculated spectra of α- or β-**6·7** are no longer near mirror images (see Figure 11). The positions of the extrema in the two spectra are almost the same and the signs are inverted, but the positive branches are more intense than the negative parts.

Since both signals lack symmetry, our initial assumptions assigning the signal above 280 nm to the enantiofacial preference and the band at 260 nm to a general reordering phenomenon were shown to be false. Instead, we presumably see the overlapping of the spectra of α and β complex, since NMR studies of the closely related phenyl-substituted system **5** showed that both diastereomers of the caffeine (**7**) complex were present at a 1:1 ratio in solution.[14] The combination of both spectra with the assumption of an equimolar mixture best describes the strong increase in signal intensity at 260 nm as well as the negative shift at 280 nm.

Signal intensities and diastereomeric excess: In all simulations the calculated CD intensities were significantly elevated with respect to the experimentally measured data (see scaling in Figure 11), which may be due to several factors. However, the systematic error caused by the spectral calculation can be estimated from the simulations of the empty tetralin system **6**, yielding a factor of about two. The general binding constant (including both diastereomers) has to be taken into account as well. After extrapolation of the observed spectra to 100% complex formation, the same scaling factor of about two can be derived from the spectra of **6·7** (Figure 11). The third contribution is the amount of enantiofacial discrimination, which reduces the signal intensity by partial cancellation of the inverse spectra. If it is assumed that the systematic error determined for **6·7** can be transferred to other systems, the ratio of the corrected calculated and experimentally measured values corresponds to the diastereomeric excess (d.e.). For menthyl-derived **4·7** we were able to calculate a d.e. of approximately 30%, while from NMR studies we were able to estimate a $\Delta G_{\alpha\beta}$ value of 1.7 kJ mol^{-1}, which would give a similar d.e. The significantly higher CDs for the menthyl-derived systems **2** and **3** indicate a high d.e. that may be far beyond 90%. However, these results should not be overemphasized since several assumptions have to be made, but the consistent character of the

results in comparison with the low-temperature NMR data is striking.

The results presented imply the development of a simple rule for interpretation of the CD spectra with respect to the preferential orientation: for the receptor systems with aliphatic substituents, a positive sign of the CD at 280–290 nm indicates the α form, whereas a negative sign implies the β isomer. Since it would be helpful to derive a generalized rule comparable to that of Harata and Kodaka, we investigated the relevant electronic interactions.

The calculated line spectra for single structures (see Figure 5) show that the strong transition of the triphenylene ketal near 280 nm is energetically close to the first π–π* transition of the guest molecules. This should give rise to some exciton coupling. Analysis of the excitations reveals a quite complex situation: the relevant transition dipole moments of 1,3,7-trimethyl uric acid (**11**) and caffeine (**7**) are almost orthogonal to each other (see Figure 4). Given that the triphenylene–guest arrangement is comparable both in bound face and in relative position, coupling with a single transition dipole moment of the triphenylene should lead to significantly different CD signals.[42] However, the signal of the triphenylene ketal at 280 nm originates from a degenerate *E* transition with two orthogonal transition moments. Thus, similar exciton coupled states for the two different guests can be formed with either of the *E* components, leading to similar spectra for the same absolute stereochemistry (i.e., α/β). Since the threefold symmetry of the triphenylene is broken by complex formation between the guest and the triphenylene, the *E* transition moments will then be aligned in a specific manner. This renders the situation too complex for derivation of a simple rule of general applicability. However, for the oxopurines the strong correlation between the sign at 280 nm and the orientation of the guest seems to be comprehendible (Table 3).

Table 3. Preferred enantiofacial orientation of the guest inside the receptor.

Guest	Receptor	X-ray[14]	CD
7	**2**	α	α
7	**3**	α	α
7	**4**	β	β
7	**5**	1:1	1:1
7	**6**	–	1:1
8	**3**	–	α
8	**4**	–	β
10	**2**	–	β
10	**4**	–	α[a]
11	**3**	–	β
11	**4**	–	α
11	**5**	–	β

[a] Weak signal prevents unequivocal assignment.

Conclusion

Enantiofacial discrimination of a single heterocyclic molecule by chirally modified triphenylene ketals has been demonstrated for the first time in solution at ambient temperature. Both, the chromophore (triphenylene) and the chiral information (urea substituents) are located in the same molecule, but CD activity is only observed when a prochiral guest is bound in a stereoselective fashion. This event transmits the chiral information to the chromophore. Such self-induced CD (SICD) reveals enantiomorphous π–π interactions for completely different receptors if the chiral moieties display inverse steric demand. This underlines that the enantiofacial discrimination is purely based on repulsive interactions. Appropriate variations in the local steric demand close to the hydrogen bonding acceptors of the guest invert the face selectivity and create further evidence for the enantiofacial differentiation.

By use of molecular dynamics simulations in conjunction with quantum chemical methods it has been possible to obtain very good agreement between the theoretical and experimentally measured CD and UV spectra. With these methods we have been able to show for the alkyl-substituted systems that there is a direct correlation between the sign of the main CD signal at 280–290 nm and the preferential position of the oxopurine guests. The shape of the remaining spectrum is strongly dependent on the guest and its precise position. Spectra could also be simulated for more complex systems bearing additional chromophores in chiral building blocks. As demonstrated in Table 3, the observed preferences were highly consistent with the available X-ray data.

While the development of new receptor systems for use as chiral templates in enantioselective reactions is still proceeding, these tools should help to make and assert efficient predictions on the behavior in solution. This should allow the rational design of novel catalysts based on these systems.

Experimental Section

CD spectra: All measurements were performed in analytical grade CH_2Cl_2. Stock solutions of all receptors and all guest molecules except for 1,3,7-trimethyluric acid were also prepared with CH_2Cl_2. Because of solubility problems the stock solution of 1,3,7-trimethyluric acid was prepared in a CH_2Cl_2/MeOH 1:1 mixture. After mixing of this solution with the different receptor molecules, the solvent was removed in high vacuum and the residue was afterwards redissolved in CH_2Cl_2.

The ligand concentration was 1.2×10^{-5} M (**4**) or 1.0×10^{-5} M (all others). Two equivalents of 1,3,7-Trimethyluric acid were added, for all other guests 10 equivalents were used to obtain sufficiently strong signals. Titrations were performed as batch titrations with constant receptor concentrations of 1.0×10^{-5} M.

The spectra were recorded on a Jobin–Yvon Dichrograph CD6 in a 1-cm quartz cell. For the measurement, five spectra were acquired and afterwards averaged.

Determination of binding constants: The binding constants were calculated by use of SPECFIT 3.0 (Spectrum Software Associates).[43] The applied model assumed the receptor and the complex as the only "colored" species, since pure caffeine shows no CD. This postulation was supported by the existence of several isosbestic points. Formation of a dimeric aggregate of the receptor was neglected since the aggregation constants determined for comparable derivatives were too small to have significant influence at the given concentrations. The spectral data between 240 and 340 nm were used for the fitting procedure.

Synthesis

1,3-Dimethyl-7-(1,1-dimethylethyl)-3,7-dihydro-1*H*-purine-2,6-dione (9): Theophylline (3.0 g, 16.6 mmol) was ground with tetrabutylammonium bromide (150 mg, 0.47 mmol) and potassium hydroxide (1.3 g, 23.2 mmol). The mixture was transferred into a flask and heated for 2 h at 135 °C. At room temperature, the resulting solid was crushed, transferred to a sealed tube, and combined with 2-bromo-2-methylpropane (9.3 mL, 11.3 g, 82.1 mmol). After 12 h at 110 °C the suspension was transferred with dichloromethane into a flask. After evaporation of the volatile components, the crude mixture was adsorbed on silica gel with the aid of hot ethanol (50 mL). Chromatography on silica, with mixtures of dichloromethane/methanol (98:2→97:3) as eluents, yielded the colorless product.

Yield: 0.75 g (3.26 mmol, 19 %). R_f = 0.50 (CH_2Cl_2/MeOH 95:5); m.p. 197–199 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40 (s, 9H; $C(CH_3)_3$), 2.09 (s, 3H; N3−CH_3), 3.65 (s, 3H; N1−CH_3), 6.67 ppm (s, 1H; 8-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.32, 30.52 (N1-C, N3-C), 30.02 (C-11), 60.17 (C-10), 108.8 (C-5), 142.0 (C-8), 152.04 (C-4), 153.04 (C-2), 154.88 ppm (C-6); IR (KBr): $\tilde{\nu}$ = 3327 (w), 3152 (m), 3016 (m; C8-H), 2987, 2949, 2885 (s; $C_{aliph.}$−H), 1594 (s), 1518 (s), 1433 (s), 1287 (m), 1201 (s), 1013 (s), 973, 924, 869, 792 (w; C8−H), 769, 748, 699, 640 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 236.2 (15) $[M]^+$, 180.1 (100) $[M-C_4H_8]^+$, 123.0 (15) $[M-C_4H_5N_2O_2]^+$, 57.1 (11) $[C_4H_9]^+$; elemental analysis calcd (%) for $C_{11}H_{16}N_4O_2$ (238.29): C 55.92, H 6.83, N 23.71; found: C 55.88, H 6.49, N 23.52.

Acknowledgements

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[41] During MCSD simulations the guest occasionally performed extreme movements, including rotations by 120° inside the host or a temporary exterior binding involving only two urea moieties. In these cases the dihedral angle was calculated from the longest phase with a centered guest molecule.
[42] Given the extreme case that caffeine were positioned in such a fashion that the electronic transition dipole moment μ(guest) were parallel to that of the host μ(host), no CD couplet would be obtained. Positioning of 1,3,7-trimethyluric acid in the same orientation would lead to a strong CD signal, since the orthogonal orientation of μ(guest) and μ(host) would cause a resulting magnetic transition dipole moment parallel or antiparallel to the resulting electric transition dipole moment.
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