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Edge-to-Face CH/π Aromatic Interaction and Molecular Self-Recognition in *epi*-Cinchona-Based Bifunctional Thiourea Organocatalysis

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Dedicated to Professor Csaba Szántay on the occasion of his 80th birthday

Abstract: The impact of cooperativity between intermolecular interactions is demonstrated by the molecular self-recognition properties of highly enantioselective *epi*-cinchona bifunctional thiourea organocatalysts. Low-temperature NMR experiments in inert solvents have revealed two sets of nonequivalent resonances in equal population for thiourea-modified members of the *epi*-quinine and *epi*-quinidine families. In solution, the predominance of an asymmetric (C_1) dimeric self-assembly with noteworthy structural motifs became evident: simultaneous intra- and intermolecular thiourea hydrogen bonding and a CH/π interaction were observed. Both the stereochemical and the diverse conformational features of the system favor the observed quinoline T-shaped aromatic π–π stacking interaction. The structure findings are supported by quantitative proton–proton distance data that were available from NOE buildup curves. The 3D structure of the dimeric assembly has been modeled in agreement with the H–H distance restraints. Owing to the geometrical preference associated with the dimerization process, the self-assembled bifunctional system is interpreted as a charge-transfer complex with the potential for catalyst self-activation.

Keywords: hydrogen bonds · molecular recognition · organocatalysis · self-assembly · stacking interactions

Introduction

Asymmetric organocatalysis has emerged as a frontier in the field of organic chemistry.[1] As might be expected for this biomimetic approach, much of the inspiration and origins in organocatalyst design comes from the chemistry found in enzymes,[1b,2] for example, the well-arranged multifunctionality and the importance of H-bonds in the catalytic cleft. Awareness of these key design elements led to the development of several useful bifunctional organocatalyst systems. Among them, the bifunctional thiourea organocatalysts[3] excel as remarkably general and highly enantioselective catalysts for a broad range of chemical reactions, including Michael additions,[4] Strecker reactions,[5] and Mannich reactions.[6] The mechanism of these catalytic processes is the subject of intensive research with experimental methods and theoretical calculations.[5d,7] Despite these advances and the broad interest in bifunctional organocatalysis, several issues remain unsettled. One major problem that seems to hamper the in-depth knowledge of the mechanism and further catalyst design is the lack of structural information, including conformational states and dynamics, about the catalysts in solution. Furthermore, the fact that bifunctionality is also a potential source of self-recognition of the catalysts has not received much attention.[8] However, there appear to be numerous practically and theoretically important aspects of this phenomenon. First, the accessibility of active catalytic sites may be influenced. Second, if noncovalent interactions favor geometrically very specific assemblies, a different level of structure study becomes attainable: the main structural features of a catalyst can be studied under equilibrium conditions. This allows one to identify conformational features

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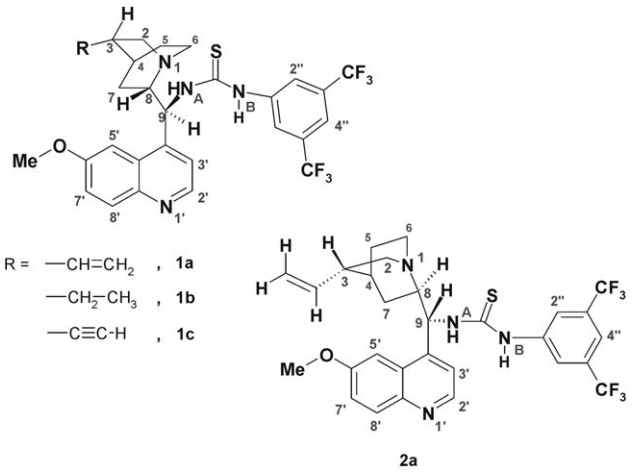
that can model the active site of the catalyst. Finally, any rare instance of a homochiral self-assembly discovered for an enantiopure alkaloid derivative is likely to initiate further research towards applications based on chiral molecular recognition in supramolecular chemistry.[8a,9]

With these aims in mind, we initiated a program to investigate this neglected aspect of organocatalysis by using detailed NMR studies to obtain accurate structural information about potential conformers and possible self-assemblies. In this paper, we present NMR studies of four cinchona-based bifunctional thiourea organocatalysts, **1a–c** and **2a** (Scheme 1), developed in our group recently.[10] These catalysts have been exploited successfully in various homogeneous enantioselective catalytic reactions,[10,11] which makes them popular members of a "privileged" catalyst family.[12] These studies unequivocally proved a significant level of association of the catalysts in nonpolar media, even at room temperature. We explored further the molecular basis of this self-recognition phenomenon through low-temperature NOESY experiments. It appeared that the prominent structural features of the self-associate are unique cooperative intermolecular H-bonding and CH/π interactions.



Scheme 1. Bifunctional *epi*-cinchona-based thiourea organocatalysts.

Results and Discussion

Self-association of the catalyst: It is generally agreed that the role of thiourea in organocatalytic reactions is related to its hydrogen-bond-donor properties,[5,13] for which the two N–H bonds of thiourea concurrently interact with oxygen donors such as nitrones[14] or chalcones.[15] It is also known that basic amines ($:NR_3$) increase the solubility of thioureas in nonpolar solvents by promoting hydrogen bonding between the amino group and the NH groups of the thiourea.[16] When the amine is introduced as part of the thiourea catalyst to afford bifunctionality, the possibility of intra- and intermolecular hydrogen bonds is introduced. These H-bond arrays can be further complicated by the presence of the quinoline ring as a possible basic and π-donor site in cinchona derivatives **1a–c** and **2a**. Despite the several possible interaction sites owing to this multifunctionality, the low-temperature solution ^{1}H NMR experiments revealed spectra of highly organized structures for **1a–c** and **2a** (Figure 1.).

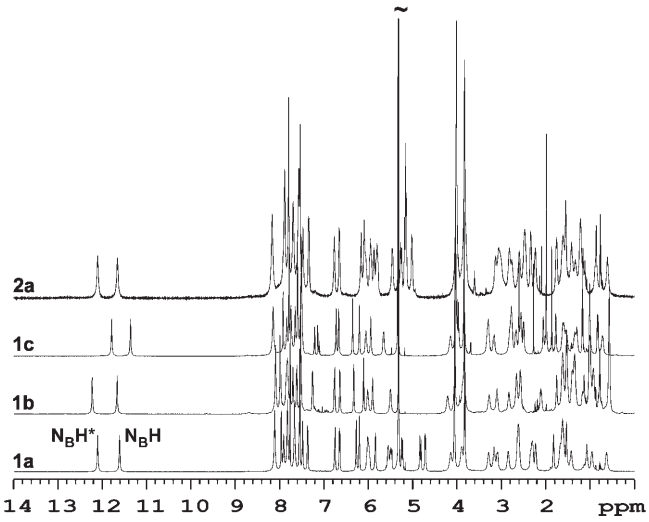


Figure 1. The low-temperature ^{1}H NMR spectra of **1a–c** (−80 °C) and **2a** (−94 °C) in CD_2Cl_2 (599.9 MHz, 30 mmol).

A common feature of these spectra is the appearance of two sets of resonances in equal (1:1) population, which is in contrast with the results of the room-temperature experiments (see Figure S1 in the Supporting Information). Both the aromatic and the aliphatic signals are doubled and there appear to be two sharp highly deshielded protons at $\delta \approx 12$ ppm, a feature that may indicate twofold thiourea hydrogen bonding. Signal doubling of this kind is rationalized by the formation of an asymmetric self-assembled dimeric system. Alternatively, the simplest interpretation would be a balanced conformational equilibrium within the monomeric species, but this option will be ruled out by the complete ^{1}H-NOESY NMR spectra (see below). Qualitatively, the resemblance of the proton spectra in Figure 1, as well as the cross-peak patterns of the ^{1}H-NOESY spectra for **1a–c** (see the Supporting Information), suggests that the three *epi*-quinine derivatives adopt structurally very similar assemblies. The self-assemblies are held together by intermolecular forces, among which hydrogen bonding is predicted to be the strongest. The "pseudoenantiomer" **2a** also forms a dimeric assembly, although it assembles at a lower temperature (−94 °C). This indicates that the nature of the assemblies is such that the stereochemical difference between **1a** and **2a** does not induce the breakdown of self-recognition.

As expected, signal doubling diminished completely in the oxygen-donor [D_8]tetrahydrofuran ([D_8]THF; −80 °C) due to the competition for hydrogen bonding. Experiments in the π-donor [D_8]toluene (−80 °C) resulted in more broadened resonances than those in CD_2Cl_2, a result that antici-

pates a certain role for π–π interactions in the assembly formation. It follows from the thermodynamics of self-association that the monomeric **1a** species should be in equilibrium with the dimeric [**1a**···**1a***] form over a broad temperature range. At room temperature, however, the ^{1}H NMR spectrum shows only one resonance set with broadening effects that suggest the presence of the underlying self-association phenomenon. The most affected resonances are those of H2′, H9, and H5′. At intermediate temperatures (−50 to 0 °C), broad ^{1}H resonances are observed due to the superposition of both intra- and intermolecular exchange processes (see the Supporting Information). The appropriate temperature range for the investigation of the self-assembly structure is in the slow-exchange regime at around −80 °C. To establish a 3D model of the self-assembly, we have undertaken a NOESY study of **1a–c** by low-temperature two-dimensional NMR methods.

Structural features of the self-assembly: The above preliminary NMR experiments encouraged us to explore the 3D structure of the self-assembly [**1a**···**1a***] by exploiting H–H distance information from NOESY experiments at −80 °C. Figure 2 shows the structure model, which is fully consistent with the set of low-temperature 2D NMR data (see the Supporting Information). It is a self-assembled dimer held together by cooperative intermolecular forces. There are a few interesting features of this dimeric geometry that make it unique. First of all, it exhibits asymmetric thiourea hydrogen bonds, namely one intra- and one intermolecular $\mathbf{N_BH}$···:**N**-type contact. Furthermore, the assembly is stabilized by a T-shaped π–π stacking interaction[17] occurring between the two methoxyquinoline rings. Unlike many homochiral self-assemblies with axial symmetry (C_2, C_3, etc.),[18] [**1a**···**1a***] is an asymmetric (C_1) object. The inversion center or the planar symmetry, which may be valid symmetry operations for characterizing the shape of some achiral hydrogen-bonded[19] and predesigned[20] self-assemblies in solution, are not applicable for the given case. The two sets of chemically nonequivalent proton resonances seen for the enantiopure compound strongly suggest a conformational difference between the two halves of the dimer. For practical reasons, in the treatment of this conformational asymmetry, an asterisk (*) will be used to distinguish the "south" molecular unit from the "north" one in Figure 2.

Another particularly important characteristic of the T-shaped aromatic-stacking motif is that it unravels the organizational role of the methoxyquinoline moiety that occurs in cinchona alkaloids. The importance of this π-donor system in enantioselective reactions has been well described.[21] In our case, the quinoline unit that has the hydrogen-bond-acceptor nitrogen atom N1′* is oriented towards the relatively electron-dense area beneath the second quinoline ring. A self-assembled charge-transfer complex with an aromatic CH/π interaction[22] is formed, in which the H-bond acceptor (in the "south" unit) is partially positive whereas the H-bond-donor part of the dimer (in the "north" unit) is partially negative (Figure 3). The weak attractive and charge-transfer nature of the CH/π interaction has been anticipated by theoretical studies for small-sized π systems,[23] benzene,[24] and other aromatics.[25] These weak T-shaped aromatic interactions, however, may significantly control the conformation and molecular-recognition properties of larger molecular systems.[26] Numerous instances of CH/π interactions have been found in the solid state by X-ray crystallography and a pivotal organizing role has been assigned to this interaction in supramolecular chemistry.[27]

In solution, the interaction is often referred to as T-shaped or edge-to-face π–π stacking if it occurs between

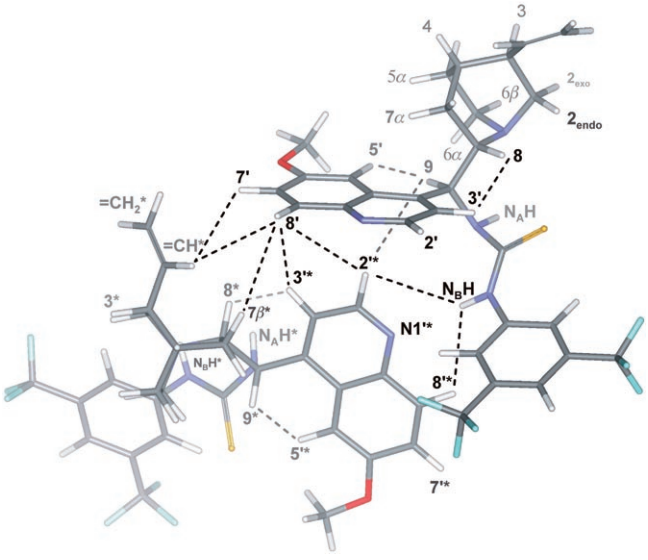


Figure 2. The dimeric structure of **1a**. The characteristic NOE contacts are indicated by dashed lines. The asterisk (*) is used to distinguish assignments in the "south" part of the dimeric assembly. For H–H distance details, see Table 1.

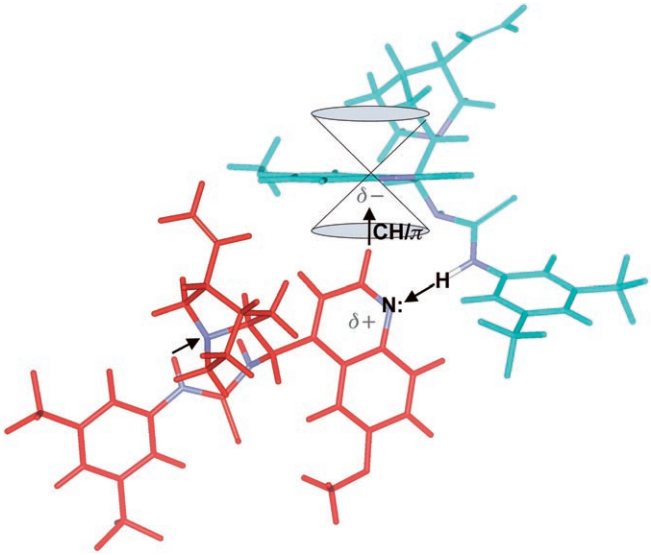


Figure 3. A side view of the dimeric assembly [**1a**···**1a***] with the CH/π interaction clearly shown.

aromatic systems. According to NMR studies, intramolecular T-shaped π–π stacking interactions exist in various predesigned model systems,[28] whereas intermolecular occurrences have mainly been reported for heterogeneous systems, such as mixtures of solvents[29] and multicomponent self-assemblies.[30] The cooperation of hydrogen bonds is frequent for cavitands and their inclusion complexes.[31] The emergence of aromatic CH/π interactions in enantiopure chiral organocatalysts is not commonplace. In the following section, we present proof of the structure of the dimeric self-assembly in which the coincidence of asymmetric thiourea hydrogen bonding, a T-shaped π–π interaction, and steric effects lead to an unprecedented molecular self-recognition phenomenon.

Proof of the structure: The geometry of the dimeric self-assembly [**1a**···**1a***] in Figure 2 was constructed solely by invoking experimental proton–proton distance (NOE) restraints in molecular modeling[32] (Table 1). In this section, we show that the refined structure is also in agreement with important torsional-angle (from *J* coupling) and chemical-shift data. Owing to the slow molecular tumbling of the [**1a**···**1a***] complex at −80 °C, the system was found to be deep in the negative NOE regime, where cross-relaxation for protons is highly effective[33] while chemical exchange is negligible. We utilized this to perform the quantitative H–H distance determination by constructing NOE buildup curves from a series of NOESY experiments recorded with short incremented mixing times (see the Supporting Information). The H–H distances that were applied as NOE restraints are listed in Table 1. To facilitate understanding of the proof of the dimeric assembly, the most conclusive NMR facts will be summarized in the following paragraph.

Table 1. The measured H···H distances that were applied as NOE restraints.

Proton pairs	H···H [Å]	Proton pairs	H···H [Å]
H8*, H3′*	2.2	N_BH, H2′*	3.0
H9*, H5′*	2.1	N_BH, H8′*	2.6
N_BH*,$H2_{exo}$*	2.5	H8′, H2′*	4.3
N_BH*, H8*	2.8	H8′, H3′*	3.8
N_BH*, $H6_\beta$*	2.5	H8′, $H7_\beta$*	2.9
H8, H3′	2.5	H8′, =CH*	3.1
H9, H5′	2.0	H7′, =CH*	2.9
H9, H2′*	4.3	H9, H2′*	4.3

In the low-temperature experiments (−80 °C), **1a** appeared to be conformationally rigid in both molecular units of the assembly with respect to rotation about the C4′–C9 and C9–C8 bonds. The H9–H5′ and H8–H3′ distances are rather short (<2.5 Å) and the H9 and H8 protons are in a *trans* conformation in both units of the dimer. These intraunit NOEs also established the connection between resonances in the two sets of quinoline/quinuclidine pairs. Several intramolecular NOE patterns ran parallel within the rigid quinuclidine moieties of the system. To extract important interunit NOEs, we searched for alterations in the NOESY cross-peak patterns. The two hydrogen-bonded thiourea proton resonances (N_BH and N_BH*) at $\delta \approx 12$ ppm give rise to two markedly different NOE patterns (see the Supporting Information). The downfield-shifted N_BH* proton signal shows intraunit H–H contacts only. Its major NOE enhancements involve correlations to the aliphatic protons (H2*, H6*, H8*) neighboring the N_1* nitrogen atom. In sharp contrast to this, N_BH has short interunit contacts to the quinoline H2′* and H8′* hydrogen atoms surrounding the N_1′* nitrogen atom and no proximity to its "own" quinuclidine nitrogen atom (N_1) and the corresponding neighbors (H2, H6, H8). This is a strong indication that only those structural models that exhibit asymmetric hydrogen bonding are valid. The nature of hydrogen bonding was explored in more detail for **1b**, because we introduced selective ^{15}N isotope labeling at positions N_B (and N_B*) to verify that hydrogen bonding is established through the thiourea N_BH forms. The pertinent resonances of the labeled compound [$^{15}N_B$]-**1b** in both the ^1H and ^{15}N spectra became doublets ($^1J(^1H,^{15}N) = 80$ Hz), which is characteristic of S=C–^{15}N–H moieties and rules out presence of the tautomeric forms (H–S–C=N). Slow molecular reorientation at −80 °C induced the TROSY effect[34] on the selectively labeled ^{15}N–^1H doublets of [$^{15}N_B$]-**1b** (see the Supporting Information), which manifested in the differential line widths of the *J*-coupled doublets.

To satisfy the condition of intermolecular N_BH···N1′* hydrogen bonding, as well as the conformation preference of the C–C bonds around the C9 and C9* atoms, the two quinoline moieties adopted the T-shaped π–π stacking. The emergence of the H2′* resonance in the aromatic region of the ^1H NMR spectra has provided a fascinating proof of this concept. The unusually shielded H2′* proton signal in Figure 4 (almost 2 ppm upfield relative to the H2′ resonance) is unequivocally due to the ring-current effect of the "north" quinoline ring in the T-shaped geometry (Figure 3). We note that the chemical-shift information in this particular case is compelling evidence because constitutionally identical hydrogen atoms are being compared. Similar shielding effects have been described recently for the intramolecular case.[28f] Independently, the T-shaped motif of the assembly is also supported by further interunit H–H NOE contacts between the CH=CH_2* group and the H7′/H8′ protons. These H–H* contacts persisted with the CH_2–CH_3* moiety of **1b** as well, but were never detected in the opposite direction (that is, between CH=CH_2 and H7′*/H8′*). Most of these important NOE contacts are depicted in Figure 2.

Finally, the appearance of the H9 and H9* multiplets merit some further comment because the different multiplicities of these resonances are also indicative of the geometry of the self-assembly. As delineated by the modified Karplus equation,[35] the vicinal couplings are torsional-angle dependent and the maximum coupling ($J \approx 9$ Hz) is expected in the *trans* conformations, whereas smaller ($J < 3$ Hz) couplings are predicted for the *gauche* conformers.[36] Being *trans* to the neighboring H8 and H8* hydrogen atoms, the

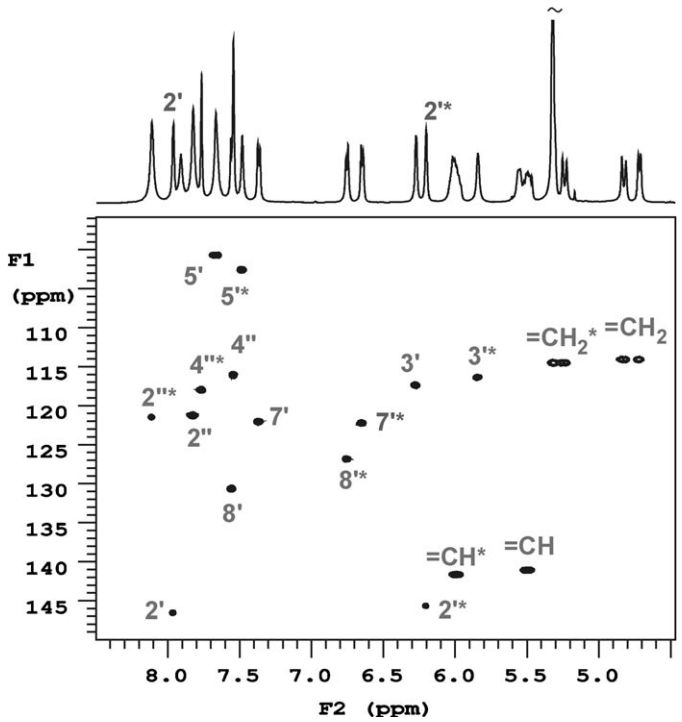


Figure 4. Partial ^{1}H–^{13}C-gHSQC experiment showing proton–carbon one-bond correlations for the complex [**1a**···**1a***] (599.9 MHz, −80 °C, 30 mmol, CD_2Cl_2). The chemical shift of the H2′* resonance is indicative of the CH/π interaction.

H9 and H9* protons both carry one large ($J \approx 8$ Hz) coupling each. Whereas the H9 signal has a doublet appearance because of this, H9* has a second large coupling ($J \approx 8$ Hz for H–C9*–N_A*–H) and the signal is therefore a triplet. This effect is best viewed with compound **1b** where the pertinent spectral region is well resolved (Figure 5). It follows that H9* is *trans* to N_AH*, whereas H9 should be *gauche* to N_AH. The additional *trans* coupling is also manifested in the extra cross-peak between the signals for H9* and N_AH* in the ^{1}H–^{1}H-COSY spectrum of **1a** (see the Supporting Information) while there no similar correlation can be found for H9. The model in Figure 2 built primarily on the basis of H–H distance restraints successfully returns these conformational preferences. It seems to be a condition of the molecular self-recognition process to have the above-demonstrated conformation alteration for the thiourea part.

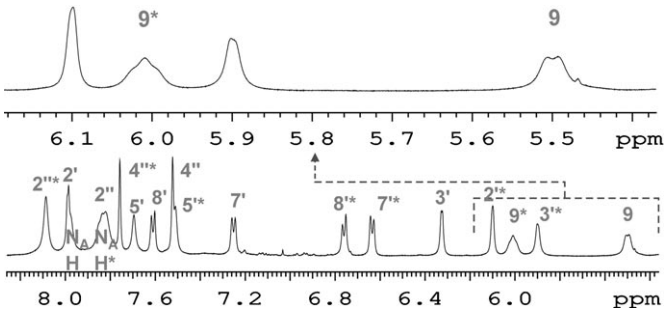


Figure 5. Partial ^{1}H NMR (599.9 MHz, −80 °C, 30 mmol, CD_2Cl_2) spectrum for the complex [**1b**···**1b***], which shows the different multiplicities for protons H9 and H9*.

Thermodynamic parameters of the assembly formation: Our efforts to determine the enthalpy and entropy changes (ΔH, ΔS, respectively) of the self-assembly process through determination of the temperature dependence of the dimerization equilibrium constants, K, over a sufficiently broad temperature range, failed in dichloromethane. Both line-shape analysis and magnetization-transfer experiments[37] were not applicable to the system owing to excessive monomer/dimer signal overlap, as well as the rapid transverse relaxation ($T_2 = 10$–30 ms) in ^{1}H NMR spectroscopy. ^{19}F NMR spectroscopy suffered strong signal overlap in CD_2Cl_2 and sensitivity problems occurred in ^{13}C NMR spectroscopy. The only viable method proved to be ^{19}F NMR detection in [D_8]toluene for **1b**.

Fortunately, the CF_3 resonances of the dimeric and the monomeric species appeared sufficiently separated to afford calculation of the K value through integration of the pertinent resonances (Figure 6). The Eyring plot ($\ln K$ versus T^{-1}) yielded the values of $\Delta H = (-36.4 \pm 1.5)$ kJ mol^{-1} and $\Delta S = (-87 \pm 7)$ J mol^{-1} K^{-1} for the dimerization process (for details, see the Supporting Information). The extrapolated ΔG values indicate that the dimeric self-assembly should be abundant near room temperature, although fast exchange determines the appearance of the proton spectra. The productivity of organocatalytic reactions is reported to be highest in nonpolar solvents (for example, dichloromethane or toluene) so one may conclude that the self-assembled species plays an important role in catalyst self-activation through a protonation/deprotonation[38] mechanism. This notion is in complete agreement with the recent observation made for proline catalysis that the self-assembly of organo-

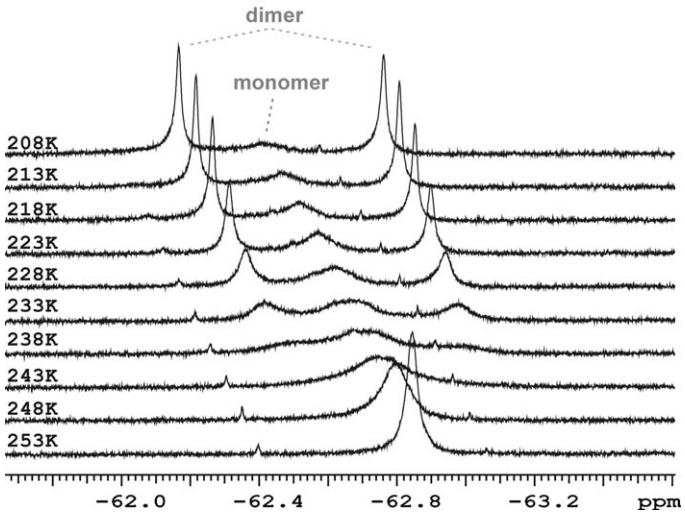


Figure 6. Temperature-dependent ^{19}F NMR (564.2 MHz) spectrum of **1b** (0.3 mmol) in [D_8]toluene.

catalysts increases the productivity and enantioselectivity of the reactions.[39]

Molecular recognition in a host–guest system: An important salient feature of the assemblies of **1a–c** is that they are the subject of intermolecular exchange and the monomeric halves should have a high tendency to act as recognition elements. In order to further verify the structural reasons for the cooperation between the thiourea hydrogen bonding and the CH/π interaction, we tested systems **1a–c** for their ability to bind 6-methoxyquinoline (MeOQ). According to the model in Figure 2, the T-shaped aromatic π–π interaction between the two methoxyquinoline rings is specifically assisted by the $N_BH\cdots{:}N$ hydrogen bond. As expected, when MeOQ was added to **1b**, all of the sharp ^1H resonances became broader; this indicates interaction between **1b** and MeOQ (three-site exchange for **1b**). An additional hydrogen-bonded thiourea N_BH proton signal, related to the [**1b**···MeOQ] heterodimer, appeared at $\delta \approx 11.6$ ppm (Figure 7). Although an excess of MeOQ did not completely

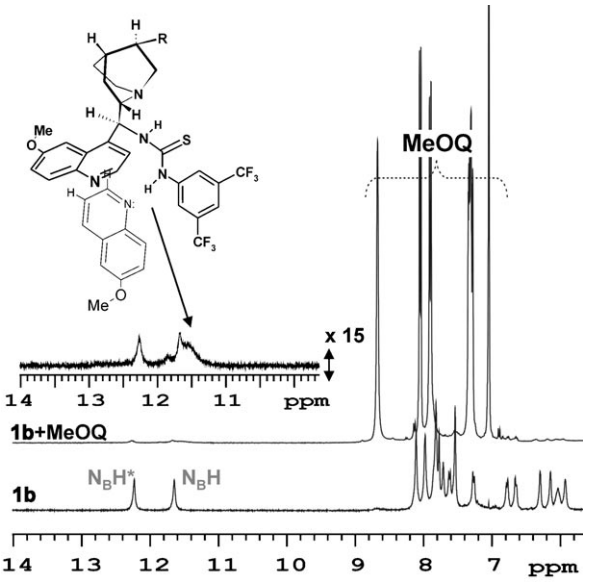


Figure 7. Partial ^1H NMR (599.9 MHz) spectra of pure **1b** (lower) and **1b** doped with 6-methoxyquinoline (**1b**+MeOQ, upper) in CD_2Cl_2 at −80 °C.

suppress the formation of the dimeric species, it is likely that the thiourea-modified *epi*-cinchona systems possess the ability to recognize heteroaromatic π systems. Their catalytic sites for capturing intermediates of enantioselective reactions may equally be around the basic quinuclidine nitrogen atom or below the electron-dense π system of the quinoline ring owing to the conformational flexibility of the thiourea part.

Conclusion

Unique self-association equilibria have been identified for recently developed *epi*-quinine (**1a–c**) and *epi*-quinidine (**2a**) based thiourea bifunctional organocatalysts. Low-temperature solution NMR experiments unraveled an asymmetric dimeric self-assembly with the coincidence of the notable structural features of aromatic edge-to-face (T-shaped) π–π stacking and asymmetric thiourea hydrogen bonding. In addition to these interactions, the molecular self-recognition of the enantiopure catalysts is brought about by the conformation diversity of the thiourea part. Although simultaneous hydrogen bonding and π–π stacking are the most fundamental intermolecular interactions in nature,[40] their relevance for small-sized organic molecules arises from the role played in spontaneously induced enantioselective chemical reactions. The focus of future research will be to explore whether the successful bifunctionality and enantioselectivity of the catalysts is embedded in the conformational features of the proposed noncovalent dimer.[41] The estimated enthalpy and entropy changes of the self-association process suggest that the charge-transfer assembly is also abundant at room temperature. The results indicate that bifunctionality is a potential source of molecular self-recognition, and extensive work needs to be done to recognize the influence of this on the productivity of reactions. The unraveled structural features of the dimeric assembly will influence our thinking on the mechanism of organocatalytic reactions and, in particular, on preferences in the capture and activation of reactants (the finding of active sites). When it is observed that oxygen-donor solvents suppress both the amount of self-assembly and the productivity of the organocatalytic reactions, it is likely that the cooperation between intermolecular forces significantly helps in promoting the reactions. Complexation studies with 6-methoxyquinoline indicated that the molecular-recognition phenomenon can also be extended to host–guest systems. This can be utilized in several fields of chemistry and chemical analysis, like heterogeneous catalysis[42] or the separation sciences.[21c–e]

Experimental Section

Compounds **1a–b** and **2a** were prepared by following the synthetic route described previously.[10,11v] Hydroquinine, quinine, quinidine, and diisopropylazodicarboxylate were purchased from Fluka. Diphenylphosphorylazide and 6-methoxyquinoline were purchased from Aldrich. 9-amino-9-deoxy-*epi*-hydroquinine was prepared as described in the literature.[10] THF was distilled from sodium/benzophenone prior to use. Exact-mass (HRMS) spectra were recorded on a VG ZAB2-SEQ tandem mass spectrometer. For thin-layer chromatography, Merck silica gel 60 (F254, 2 mm, 20×20 cm) was employed. Procedures have not been optimized and yields are low due to hydrolysis of the CF_3 groups in the acidic aqueous medium. The NMR experiments were carried out on 400 MHz (for ^1H) Varian Inova and 600 MHz (for ^1H) Varian NMR System spectrometers by using 5 mm direct detection ^{15}N–^{31}P/{^1H–^{19}F} probes equipped with a *Z* pulse field gradient. ^1H chemical shifts are referenced to residual solvent signals (CD_2Cl_2: $\delta = 5.32$ ppm; [D_8]toluene: $\delta = 2.09$ ppm (Me)). Deuterated (99.98 atom %) solvents were purchased from Merck GmBH (Germany). ^{15}N NMR spectra were recorded by using a 5 s recy-

cle delay and Waltz gated proton decoupling during acquisition. The ^{15}N and ^{19}F NMR chemical shifts are referenced to nitromethane ($\delta_{CH_3NO_2}=0.0$ ppm) and $CFCl_3$ ($\delta_{CFCl_3}=0.0$ ppm), respectively. Spectra were processed with the VnmrJ 2.1B software. All two-dimensional spectra were by using the Varian standard spectrometer pulse-sequence library. In low-temperature ^{1}H-NOESY experiments, solvent presaturation was used during the recycle delay. 6012 complex data points were acquired in the F2 dimension and 320 complex data points in the F1 dimension. Spectral widths of 16 kHz were used in both dimensions and the relaxation delay time was 1.2 s. NOESY mixing times of 5, 10, and 20 to 150 ms were used. Data were multiplied by Gaussian weighting functions and zero filled to a 8192×4096 matrix. Digital resolution in the F1 dimension was doubled by twofold linear prediction. An automated polynomial baseline correction was used. All spectra were referenced to residual solvent signals in both dimensions. NOESY peak picking and volume integration was performed with the VnmrJ 2.1B software. The assignment of the NMR resonances of **1a** at −80 °C followed the regular procedure: collection and analysis of through-bond (^{1}H–^{1}H- and ^{1}H–^{13}C-COSY) and through-space (^{1}H-NOESY) correlations. The ^{1}H NMR chemical-shift indexing used to evaluate the NOESY spectra is listed in Table S1 in the Supporting Information. A total number of 514 cross-peaks was assigned in the NOESY spectra of **1a**. Parallel experiments performed on the two other derivatives **1b** and **1c** helped to verify the proposed model by unraveling analogous H–H contacts in the close structural analogues. The cross-relaxation rates, σ_{ij}, between protons i and j were determined by using the initial linear buildup of the NOE contacts. Typical buildup curves are shown in the Supporting Information. To obtain the interproton distances (r_{ij}), we determined the molecular reorientational correlation time ($\tau_c=3.35\,E^{-7}$ s) according to an invariant interproton distance ($r_{H2'-H3'}=2.5$ Å) by using Equation (1), in which μ_0 is the vacuum permeability, $\hbar$ is the Planck constant divided by 2π, γ is the gyromagnetic constant of protons, and ω is the Larmor frequency for protons.

$$\sigma_{ij}=\left(\frac{\mu_0}{4\pi}\right)\frac{\hbar^2\gamma^4}{10}\left[\frac{6\tau_c}{1+4\omega^2{\tau_c}^2}-\tau_c\right]r_{ij}^{-6} \quad (1)$$

The relevant NOE-based intra- and interunit r_{ij} values were introduced as H–H distance restraints in molecular modeling to allow refinement of the structure model. Molecular modeling was performed at the AM1 level by using HyperChem 8.0 Professional.[32] Distance restraints of 1 kcal mol^{-1} Å^{-2} were applied for each H–H contact in AM1 geometry optimization.

[^{15}N]-1-Nitro-3,5-bis(trifluoromethyl)benzene: Concentrated sulfuric acid (20 mL) was cooled to 0 °C. Oleum (65%; 5 mL) was then slowly added dropwise at 0 °C. Afterwards, $K^{15}NO_3$ (1.91 g, 18.7 mmol) was added to this mixture. 1,3-Bis(trifluoromethyl)benzene (2.00 g, 9.35 mmol) was poured into the acidic mixture. The mixture was allowed to warm to room temperature and was stirred overnight. The reaction mixture was poured onto ice and washed with CH_2Cl_2 (3×20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The nitro compound was obtained without further purification as a yellow oil (0.30 mg, 1.15 mmol; yield: 12.3%): HRMS (EI): m/z calcd for $C_8H_3F_6{}^{15}NO_2$ $[M]^+$: 260.0038; found: 260.0037; ^{1}H NMR (399.9 MHz, $CDCl_3$, 30 °C): $\delta=8.23$ (s, 1H, CH-Ar), 8.71 ppm (s, 2H, CH-Ar); ^{15}N NMR (40.5 MHz, $CDCl_3$, 30 °C): $\delta=-17.0$ ppm.

[^{15}N]-3,5-Bis(trifluoromethyl)aniline: The labeled nitro compound (0.26 g, 1.00 mmol) was dissolved in concentrated hydrochloride acid and cooled to 0 °C. $SnCl_2{\cdot}2H_2O$ (2.26 g, 10.0 mmol) was then added. The mixture was allowed to warm to room temperature and was stirred overnight. The reaction mixture was poured onto ice and made alkaline with 10% NaOH solution while being kept at 0 °C. At first, $Sn(OH)_2$ precipitated from the solution but this dissolved again upon addition of further amounts of the NaOH solution. This mixture was washed with CH_2Cl_2 (4×20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The aniline was obtained without further purification as a yellow oil (90.0 mg, 0.39 mmol; yield: 39.1%): HRMS (EI): m/z calcd for $C_8H_5F_6{}^{15}N$ $[M]^+$: 230.0297; found: 230.0296; ^{1}H NMR (399.9 MHz, $CDCl_3$, 30 °C): $\delta=4.06$ (d, 2H, $^1J(^1H,^{15}N)=82.9$ Hz, $^{15}NH_2$), 7.03 (s, 2H, CH-Ar), 7.21 ppm (s, 1H, CH-Ar); ^{15}N NMR (40.5 MHz, $CDCl_3$, 30 °C): $\delta=-320.4$ ppm.

[^{15}N]-3,5-Bis(trifluoromethyl)phenyl isothiocyanate: Thiophosgene (100 mg, 0.87 mmol) was suspended in distilled water (1 mL) and cooled to 15 °C. [^{15}N]-3,5-bis(trifluoromethyl)aniline (90 mg, 0.39 mmol) in chloroform (0.5 mL) was added to this mixture. The mixture was then stirred for 4 h. The reaction mixture was added to 10% HCl solution (10 mL) and the whole mixture was washed with CH_2Cl_2 (4×10 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The isothiocyanate was obtained without further purification as a yellow oil (50.0 mg, 0.18 mmol; yield: 47.0%): HRMS (EI): m/z calcd for $C_8H_3F_6{}^{15}NS$ $[M]^+$: 271.9861; found: 271.9865; ^{1}H NMR (399.9 MHz, $CDCl_3$, 30 °C): $\delta=7.64$ (s, 2H, CH-Ar), 7.76 ppm (s, 1H, CH-Ar); ^{15}N NMR (40.5 MHz, $CDCl_3$, 30 °C): $\delta=-271.8$ ppm.

[^{15}N]-(3″,5″-bis(trifluormethyl)phenyl-*N*′-(9-deoxy-*epi*-quinin-9-yl)thiourea ([$^{15}N_B$]-1b): A solution of [^{15}N]-3,5-bis(trifluoromethyl)phenyl isothiocyanate (50 mg, 0.18 mmol) in dry THF (2 mL) was slowly added to a solution of 9-amino-(9-deoxy)-*epi*-hydroquinine (65 mg, 0.2 mmol) in dry THF (5 mL) at ambient temperature. The mixture was stirred overnight and the solvent was removed in vacuo. The residue was purified by preparative thin-layer chromatography on silica gel (with EtOAc/MeOH/concd aq NH_4OH (300:5:1) as the eluent) to afford the ^{15}N-labeled thiourea catalyst as an off-white amorphous solid (39.1 mg, 0.07 mmol; yield: 36.4%): HRMS (EI): m/z calcd for $C_{29}H_{30}F_6N_3{}^{15}NOS$ $[M]^+$: 597.2015; found: 597.2012; ^{15}N NMR (60.8 MHz, CD_2Cl_2, −80 °C): $\delta=-246.6$, −247.2 ppm.

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