Insight into the Folding and Cooperative Multi-Recognition Mechanism in Supramolecular Anion-Binding Catalysis

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1. General Information and Materials

The (R,R)-tetrakistriazole 1 was synthesized according to a previous publication,[1] tetrabutylammonium chloride (TBACl; 97 %), tetrabutylammonium benzoate (TBAPbCO, 99 %), tetrabutylammonium triflate (TBAOTf, 99 %), acetone p.a. (99.9 %), and acetone-ds (99.9 %) were purchased from Sigma Aldrich (Germany). Catalyst 1 and all the TBA salts were stored under argon atmosphere. 1H-NMR spectra were recorded in acetone-ds (reference signal: [2] 1H = 2.05 ppm) or THF-ds (reference signal: 1H = 1.73 ppm) on a Bruker Advance 300, 400 or 500 MHz spectrometer, and on a Magritek Spinolve benchtop 60 MHz spectrometer. Binding stoichiometry Job Plot studies were carried out on a Bruker Avance 400 spectrometer. ITC studies were performed on a Nano ITC SV, TA instruments. Circular dichroism (CD) spectra were recorded on a JASCO J-815 spectrometer at room temperature.

2. Experimental Binding Studies

2.1. Non-linear Effect Study

The effect of the change in the enantiopurity of the chiral catalyst 1 on the enantioemic outcome of the model asymmetric Reissert-type reaction of quinoline with iso-propyl tert-butyldimethylsilyketene acetal as nucleophile was performed following the catalytic conditions previously reported with 5 mol% of 1[1] and examined using Kagan’s model [eneff = enemax · eecat][3]

Several enantiopurities of the catalyst (R,R)-1 ranging from $ee_{cat} = 0$ to >99% were tested, resulting in a linear correlation between $eneff$ and $ee_{cat}$ (see Scheme 1 in article). Therefore, the formation of inactive or more active aggregates was ruled out. This observation was further confirmed by conducting the same reaction with the meso-variant of 1 (derived from the cis-cyclohexane-1,2-diamine), which gave the product in 85% yield and 0% ee.
2.2. Stoichiometry Analysis

The determination of the binding stoichiometry of host:guest was performed by the Job Plot method (plotting of the $\Delta \delta$ of the relevant protons H1-H4 against the mole fraction of guest $X_G$), using solutions of 1 with the corresponding salt at varying ratios within a total concentration of 5 mM. Single-pulse $^1$H-NMR spectra were taken at 25.00 °C ± 0.05 °C. Changes of the chemical shifts relative to a solution of pure 1 were taken for construction of the Job Plot. A parabolic function was used to determine the maxima ($X_{max}$) of the Job Plots in order to determine the stoichiometry.

The plots in Figure S1 show a maximum around 0.5, which corresponds to a complex stoichiometry of 1:1 for TBACl and TBAPhCO$_2$. In the case of TBAOTf (Figure S2), no chemical shift change was measured and therefore no maximum could be determined. Thus, the Job plot does not indicate binding to TfO$^-$ under these conditions.

![Figure S1. Job Plot of 1 [5 mM] with; TBACl (left) and TBAPhCO$_2$ (right)](image)

2.3. $^1$H-NMR Titration Experiments

The anion-binding affinities of hydrogen-bond (HB) donor tetrakistriazole 1 towards different anions such as chloride, benzoate and triflate were studied by $^1$H-NMR titrations. The assignment of the selected protons to determine the binding abilities of 1 is presented below, in which H1 and H2 belong to the triazole units while H3 and H4 correspond to the protons attached to the aromatic rings (Figure S3, left). Due to the solubility problems of the corresponding TBA salts in toluene, all the experiments were carried out with a constant concentration of 1 (host) of 2 mM in acetone-$d_6$, introducing the corresponding anion as a TBA salt (guest). The $^1$H-NMR titrations were carried out with 23 or 10 data points, spanning a guest:host ratio of 0 to 10 equivalents. A representative example of the $^1$H-NMR titration of 1 [2 mM] with TBACl (23 data points, from 0 to 10 equiv.) in acetone-$d_6$ is herein presented (Figure S3).
Figure S3. Catalyst 1: X complex (left); ¹H-NMR chemical shifts (δ) of 1 [2.0 mM] in acetone-d₆ + 0.0–10.0 equiv. TBACl (right).

The preparation of the samples was performed from stock solutions of catalyst 1 (host) [5 mM or 20 mM], and TBA-salts (guest) [10 mM or 50 mM] in acetone-d₆. The samples were prepared directly in the NMR tube with a constant 2 mM concentration of 1 and a total volume of 500 µL by the addition of aliquots of the corresponding anion (TBACl) from 0 to 10 equiv. As it is shown in the ¹H-NMR spectra (Figure S1, right), the variation of the chemical shifts (Δδ) of the protons from the triazole moieties (H₁ and H₃) showed a higher downfield shift (ΔδH₁ = 1.17 ppm and ΔδH₃ = 0.97 ppm, respectively) compared with the corresponding aromatic protons H₂ and H₄ (ΔδH₂ = 0.46 ppm and ΔδH₄ = 0.16 ppm, respectively). This suggests that H₁ and H₃ are those which are more affected by the presence of the anion in the cavity of 1. The stoichiometry between catalyst 1 (host):TBACl (guest) was fitted to the 1:1 model using Bindfit software, obtaining a binding constant of 560 ± 224 M⁻¹ (Figure S4, left). This experiment was repeated three times, obtaining Kₛ of 536 ± 214 M⁻¹ as an average of all four measurements. The errors given include the fitting errors and an estimated 5% experimental error to logKₛ (Figure S4, right).

The binding affinities Kₛ of 1 to chloride and benzoate showed similar values (Figure S4 and S5), while triflate did not provide a significant binding (Kₛ = 15 ± 3 M⁻¹, when also considering a 1:1 stoichiometry, Figure S6). In the case of benzoate, the titration was performed twice (Kₛ = 605 ± 248 M⁻¹ and 794 ± 355 M⁻¹) obtaining Kₛ of 698 ± 317 M⁻¹ as an average of both values. In Figure S5 (left), one of the experiments is shown as a representative example.

Figure S4. Plot of ³¹H-NMR of 1 [2.0 mM] in acetone-d₆ + 0.0–10.0 equiv. of TBACl (left) and summary of measurements (right).
The weak binding of tetrakis(triazole) 1 towards TBACl and TBAPhCO₂ in acetone is confirmed again by ITC measurements (Figure S7). To carry out the measurements, catalyst 1 and the TBA salts were dried with a turbomolecular pump and the solutions were prepared under ambient conditions. Before measurement, all samples were degassed by sonification for 10 min. The temperature during the measurement was set to 25.0 °C and the stirring speed was 300 rpm. A salt solution of 30 mmol/L was injected to a 2 mmol/L solution of catalyst. The injection interval of the salt solution was 500 s with an injection volume of 10 μL and 24 injections in total. A blank measurement of salt solution into acetone was used to eliminate the effects of heat of dilution and background heat. After baseline correction the data were fitted assuming a 1:1 binding model according to Freire et al. From the final values of the binding constant \( K_a \) and the binding enthalpy \( \Delta H \) the free energy \( \Delta G \) and entropy \( \Delta S \) are derived. Titration experiments are repeated at least 3 times, and average values of the resulting parameters are calculated.

The raw and processed heat data are exported and analyzed by a python script. The first point is weighted as 0 for the fitting process, but is still present for all calculations before. The fitting process can now be started by giving the experimental parameters and an initial guess of \( K_a \) and \( \Delta H \) to the model function. This model calculates at first the total concentration of host and guest in the cell for each titration step \( k \) (eq. (1) and (2)). \([L]_0\) is the initial guest concentration in the syringe and \([M]_0\) the initial host concentration in the cell. \( V_{ij} \) and \( V_{vol} \) are the injection and the cell volume, respectively.

\[
[L]_T = [L]_0 \cdot \left(1 - \left(1 - \frac{V_{ij}}{V_{vol}}\right)^k\right) \quad (1)
\]

\[
[M]_T = [M]_0 \cdot \left(1 - \left(1 - \frac{V_{ij}}{V_{vol}}\right)^k\right) \quad (2)
\]

Afterwards, the free ligand concentration \([L]\) is calculated:

\[
[L]_T = [L] + [M]_T \cdot \frac{\partial \ln P}{\partial \ln [L]} \quad \text{with} \quad P = 1 + K_a \cdot [L] \quad (3)
\]
The host:guest complex concentration [ML] is then calculated for each step with the initial guess of the association constant and from this the heat per step $q_k$ with the help of the initially given enthalpy.

$$[ML] = K_a \cdot [L] \cdot ([M]_T - [L]_T + [L])$$  

$$q_k = \frac{v_{cell} \cdot \Delta H}{v_{inj} \cdot [L]_k} \cdot \left([ML]_k - [ML]_{k-1} \cdot (1 - V_{inj}/V_{cell})\right)$$

The model function now returns the heat values of each step to the fitting process and compares them to the experimental values using the least squares method. The values of $K_a$ and $\Delta H$ are refined and evaluated again until there is no further improvement in the least squares.

From the final values of $K_a$ and $\Delta H$ the free energy $\Delta G$ and entropy $\Delta S$ are derived (Table S1).

**Figure S7.** ITC raw data from titration of 30 mM of 1a) TBACl into 2 mM of 1 at 25 °C (right) and 2a) TBAPhCO$_2$ into 2 mM of 1 at 25 °C (left). b) Heat per injection (circles) and fit to determine thermodynamic parameters (line).

| 1:TBACl | 1:TBAPhCO$_2$ |
|---------|---------------|
| $K_a = 305 \pm 96 \text{ M}^{-1}$ | $K_a = 224 \pm 90 \text{ M}^{-1}$ |
| $\Delta H = -1.8 \pm 0.5 \text{ kcal mol}^{-1}$ | $\Delta H = -2.1 \pm 0.6 \text{ kcal mol}^{-1}$ |
| $\Delta G = -3.4 \pm 0.2 \text{ kcal mol}^{-1}$ | $\Delta G = -3.1 \pm 0.3 \text{ kcal mol}^{-1}$ |
| $\Delta S = 5.5 \pm 0.9 \text{ cal mol}^{-1} \text{ K}^{-1}$ | $\Delta S = 3.5 \pm 2.9 \text{ cal mol}^{-1} \text{ K}^{-1}$ |

The errors given in Table S1 are standard deviations of 5 or 6 individual measurements, which cover the experimental and the fit errors.

### 2.4. Circular Dichroism (CD) Titration

Circular Dichroism (CD) spectra of the chiral HB donor tetrakistriazole 1 were recorded to visualize the change of its spatial orientation upon titration with TBACl salt (up to 10 equiv.) as suitable chloride anion source by measuring the absorption and resulting changes [in mdeg] of polarized light (Figure S8). Due to the absorption range of the receptor 1 (220-320 nm), THF was selected as optimal solvent. The sample preparation was done similar to the NMR-titrations from stock solutions of 1 (host) [1.25 mM] and TBACl salt (guest) [1 mM or 10 mM], to reach the desired concentration of 62.5 μM.
3. Computational Studies

All static calculations were carried out with the Gaussian16 program.[6] The solvation effects were calculated with COSMOtherm software.[7] The wave function (WF) properties were studied via Natural Bond Orbital (NBO) stabilization energies with NBO package[8] and Quantum Theory of Atoms in Molecules (QTAIM).[9] Ab initio Born-Oppenheimer molecular dynamics (BOMD) simulations were performed with TURBOMOLE program.[10]

3.1. Structures

The conformer distribution search was performed in the gas phase using DFT-M062X[11] functional and the 6-31G(d,p) basis set[12] by optimization of a manually constructed number of plausible initial structures. To determine the most stable structures various dihedral angles, binding sites, and hydrogen binding patterns were modified. At the same level of theory, the zero-point energy was computed, thus each minimum was identified by the presence of all positive frequencies. Relative energies were calculated to find the most stable structures at a given temperature and solvent. Quasi-rigid-rotor harmonic oscillator (quasi-RRHO) approximation for the standard state in a solution of 1 mol/L was used to correct the erroneous entropic contribution of low vibration modes (cut off of 100 cm⁻¹) as described previously.[13] The effect of toluene and acetone at -78 °C and 25 °C were obtained with COSMO-RS theory at BP86/tzvp level of theory.[14] The most stable structures of the catalyst 1 (host) and host:guests (H:nG) complexes with Me₄NCl and Me₄NOTf as guests in toluene at -78 °C are presented in the Figure S9. Therefore, we simplify the notation to 1:n(chloride or triflate), keeping in mind that for all calculations the same cationic counterpart is explicitly treated.

Figure S9. The most stable structures of the catalyst and all studied complexes in toluene at -78 °C.
We found 11 conformers of 1 (Figure S10), 13 of 1:1(Cl) (Figure S11) and 17 of 1:2(Cl) (Figure S12), as well as 11 of 1:1(OTf) (Figure S13), 16 of 1:2(OTf) (Figure S14), and 19 of 1:3(OTf) (Figure S15) in toluene and acetone at -78 °C (in Figures S13-18, the relative Gibbs energies are given in kcal mol⁻¹). The presence of a quasi-helical structure of the catalyst 1 that forms two symmetric binding-cavities is observed. Moreover, a strong deformation of the catalyst influenced by the binding of the first guest is observed, while the capability of binding another one seems to be sterically possible.

**Figure S10.** Optimized structures of catalyst 1. Relative Gibbs free energies in kcal mol⁻¹.

**Figure S11.** Optimized structures of the 1:1(Cl) complex.
**Figure S12.** Optimized structures of the 1:2(Cl) complex.

**Figure S13.** Optimized structures of the 1:1(OTf) complex.
**Figure S14.** Optimized structures of the 1:2(OTf) complex.
We also considered the explicit effect of toluene and acetone as solvents on the structural changes of the catalyst $1$ using CPCM, IEFPCM and SMD solvation models. This effect is measured by root mean square deviation (RMSD), defined as:

$$RMSD = \sqrt{\frac{1}{N} \sum_{i=1}^{N} (r_i^{(gas\text{-}phase)} - r_i^{(solution)})^2}$$

where $N$ is the number of atoms whose position is compared, and $r_i$ is the position of $i$ atom.

The $RMSD$ between geometries in the gas-phase and the given solvation model for each of the conformers of $1$ (I-XII) is shown in Table S2. The gas-phase calculations describe accurately the geometry of all isomers in comparison with each of the solvation models. In all cases but one (isomer XII in acetone with the SMD model), the $RMSD$ is smaller than 1 Å, even for more polar solvents such as acetone. The average $RMSD$ for structural changes in toluene using CPCM, IEFPCM and SMD is smaller than for the geometries in acetone; 0.23, 0.20 and 0.35 vs. 0.42, 0.34 and 0.55 Å, respectively.
Table S2. Root mean square deviations, RMSD in Å, for the structures of 1 calculated for each solvation model with respect to the gas-phase geometries.

| Conformer | All atoms | | Backbone only | |
|-----------|-----------|---|---|---|
|            | CPCM | IEFPCM | SMD | CPCM | IEFPCM | SMD |
| **Toluene** | | | | | | |
| I         | 0.19 | 0.13 | 0.55 | 0.15 | 0.10 | 0.46 |
| II        | 0.31 | 0.43 | 0.36 | 0.27 | 0.37 | 0.32 |
| III       | 0.34 | 0.16 | 0.34 | 0.27 | 0.14 | 0.29 |
| IV        | 0.23 | 0.23 | 0.36 | 0.21 | 0.20 | 0.32 |
| V         | 0.47 | 0.09 | 0.61 | 0.39 | 0.08 | 0.52 |
| VI        | 0.40 | 0.42 | 0.15 | 0.33 | 0.33 | 0.13 |
| VII       | 0.12 | 0.21 | 0.13 | 0.10 | 0.16 | 0.10 |
| VIII      | 0.12 | 0.25 | 0.29 | 0.10 | 0.20 | 0.24 |
| IX        | 0.09 | 0.05 | 0.34 | 0.07 | 0.04 | 0.29 |
| X         | 0.10 | 0.09 | 0.28 | 0.08 | 0.06 | 0.24 |
| XI        | 0.11 | 0.11 | 0.38 | 0.08 | 0.08 | 0.32 |
| **Average** | 0.23 | 0.20 | 0.35 | 0.19 | 0.16 | 0.29 |
| **Acetone** | | | | | | |
| I         | 0.63 | 0.40 | 0.43 | 0.58 | 0.36 | 0.36 |
| II        | 0.53 | 0.54 | 0.51 | 0.47 | 0.30 | 0.46 |
| III       | 0.82 | 0.82 | 0.63 | 0.71 | 0.71 | 0.53 |
| IV        | 0.61 | 0.45 | 0.46 | 0.55 | 0.40 | 0.40 |
| V         | 0.69 | 0.32 | 0.36 | 0.58 | 0.27 | 0.30 |
| VI        | 0.50 | 0.53 | 0.67 | 0.41 | 0.44 | 0.57 |
| VII       | 0.12 | 0.19 | 1.19 | 0.10 | 0.16 | 0.72 |
| VIII      | 0.20 | 0.18 | 0.68 | 0.16 | 0.15 | 0.57 |
| IX        | 0.17 | 0.16 | 0.54 | 0.14 | 0.13 | 0.46 |
| X         | 0.21 | 0.20 | 0.31 | 0.17 | 0.16 | 0.27 |
| XI        | 0.15 | 0.16 | 0.27 | 0.12 | 0.13 | 0.23 |
| **Average** | 0.42 | 0.34 | 0.55 | 0.36 | 0.29 | 0.44 |

The effect of the larger basis set on the electronic energies (E_{SCF}) of the catalysts 1 was also checked (Table S3). The increment of the basis-functions for H atoms and adding extra diffuse functions does not provide a significant improvement. It is worth to mention that only electronic relative DFT energies give exactly reversed order of the total relative stability of the conformers (I-XI) of 1 (see Figure S10).

Table S3. The effect of the basis set on relative electronic energies (ΔE_{SCF}) of catalyst 1.

| Conformer | ΔE_{SCF} 6-31G(d,p) | ΔE_{SCF} 6-311++G(d,p) |
|-----------|----------------------|------------------------|
| I         | 0.00                 | 0.00                   |
| II        | -1.6                 | -1.8                   |
| III       | -1.7                 | -1.9                   |
| IV        | -1.7                 | -1.8                   |
| V         | -1.7                 | -1.9                   |
| VI        | -1.7                 | -2.2                   |
| VII       | -1.8                 | -2.3                   |
| VIII      | -3.4                 | -3.7                   |
| IX        | -3.4                 | -3.6                   |
| X         | -3.4                 | -3.7                   |
| XI        | -3.4                 | -4.2                   |

3.2. Binding Energies

The binding energies (BE) were computed within the super-molecular approach, defined as: BE(H:Gn) = E(H:Gn) − E(H) − nE(G), using all corrections as described in section 3.1. Additional counter-poise (CP) correction[18] to minimize the basis set superposition error arising from relatively small basis set for optimization search and amount-of-substance fraction (ω) according to Boltzmann distribution (Eq. 8) at a given temperature and solvent were included. The latter is defined as:

$$
\omega_i^i(H;G_n) = \frac{\Delta E_{i}^{(H;G_n)}}{Z^{(H;G_n)}} = \sum_i e^{-\frac{\Delta E_{i}^{(H;G_n)}}{kT}}
$$

where n is the number of guest molecules (n = (0;2) and (0;3) for CI and OTf, respectively), and ΔE_{i} is the corrected, total energy of each conformer i of a given complex (H:G_{n}). The energetic information, including the corrections used to calculate the BE is presented in Table S4.
### Table S4. Energetics calculated at DFT levels: M062X/6-31G(d,p) for quasi-RRHO corrected Gibbs energy (G), BP86/def2tzvp for solvation energy $G_{solv}$ of acetone ($G_a$) and toluene ($G_t$), and total relative energies with all corrections ($\Delta E$). Absolute energies are given in Hartrees and the relative energies in kcal mol$^{-1}$.

| Conf. | $E_{SCF}$ | $G$ | $\Delta G$ | $G_a$ | $G_t$ | $\Delta G_a$ | $\Delta G_t$ | $\Delta E$ | $\Delta E_a$ | $\Delta E_t$ |
|-------|-----------|-----|-----------|-------|-------|-------------|-------------|-----------|-------------|-------------|
|       | (-78 °C) | (-78 °C) | (25 °C) | (25 °C) | (25 °C) | (25 °C) | (25 °C) | (25 °C) | (25 °C) | (25 °C) |
| 1     |          |      |          |       |       |             |             |           |             |             |
| I     | -408.136286 | -408.253990 | 0.00 | -408.301684 | -0.112668076 | -0.09752133 | -0.09656797 | -0.08676805 | 0.00 | 0.00 | 0.00 |
| II    | -408.139515 | -408.250784 | -1.70 | -408.304061 | -0.018784658 | -0.03540824 | -0.02177707 | -0.02731114 | 1.2 | 0.8 | 1.0 |
| III   | -408.139055 | -408.256614 | -1.60 | -408.304271 | -0.107877212 | -0.09333737 | -0.09202586 | -0.08268506 | 1.5 | 1.0 | 1.3 |
| IV    | -408.138966 | -408.250727 | -1.40 | -408.303824 | -0.107862126 | -0.03989910 | -0.02917915 | -0.02689246 | 1.6 | 1.1 | 1.5 |
| V     | -408.139024 | -408.253518 | -1.11 | -408.304199 | -0.108741209 | -0.03371297 | -0.02615304 | -0.02649331 | 1.8 | 1.5 | 1.9 |
| VI    | -408.138986 | -408.256994 | -1.30 | -408.303713 | -0.106566908 | -0.02827743 | -0.02118929 | -0.02030742 | 2.6 | 1.6 | 2.1 |
| VII   | -408.139192 | -408.255926 | -1.00 | -408.303204 | -0.105852955 | -0.09213163 | -0.09066534 | -0.09159207 | 3.0 | 2.2 | 2.8 |
| VIII  | -408.141632 | -408.258794 | -0.31 | -408.306637 | -0.10257605 | -0.08882067 | -0.07829652 | -0.07831557 | 3.2 | 2.4 | 2.8 |
| IX    | -408.141638 | -408.258806 | -0.30 | -408.306515 | -0.10249721 | -0.08887377 | -0.07816079 | -0.07832621 | 3.3 | 2.4 | 3.0 |
| X     | -408.141739 | -408.258653 | -0.29 | -408.305506 | -0.10252134 | -0.08892768 | -0.07821378 | -0.07831673 | 3.5 | 2.5 | 3.2 |
| XI    | -408.141716 | -408.257785 | -0.24 | -408.304973 | -0.10212273 | -0.08998639 | -0.07866410 | -0.07847033 | 4.7 | 2.9 | 4.2 |

1. $\Delta E_a = G_a - G_solv$; $\Delta E_t = G_t - G_solv$; $\Delta E = G - G_a - G_t + G_{solv}$; $\Delta E = G - G_a$; $\Delta E = G - G_t$. 

2. $\Delta E$ is given in kcal mol$^{-1}$ and $\Delta G$ in kcal/mol.

3. $E_{SCF}$ is given in Hartrees ($E_{H}$).

4. $G$, $G_a$, and $G_t$ are given in Hartrees ($E_{H}$).

5. $\Delta E$, $\Delta E_a$, and $\Delta E_t$ are given in kcal mol$^{-1}$.
Cooperativity

The cooperativity based on the calculated binding energies (BE) is represented in the super-molecular fashion as a function of the stoichiometry (Figure S16). Three effects can be distinguished: i) non-cooperative for $2BE_{1:1} = BE_{1:2}$, ii) cooperative destructive for $2BE_{1:2} > BE_{1:2}$, and iii) cooperative synergistic for $2BE_{1:1} < BE_{1:2}$. In the case of binding (negative BE), we observe only destructive cooperativity (above the non-cooperative curve). The destabilizing interaction is reduced significantly in toluene. The synergistic effect (below the non-cooperative curve, less positive BE) is observed only for triflate as anion in acetone, however it is not strong enough to form a complex under these conditions (still positive BE).

Figure S16. Cooperative analysis for host:guest (H:G_n) based on binding energies (BE).

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3.3. Stabilization Energies

Additionally to the catalyst 1:Me$_2$NCl(guest) interactions with chloride anion presented in the main article, the effect of triflate (OTf$^-$) as anion was analyzed. The calculated unit NBO stabilization energies $E$ between the host catalyst 1 (C), anion/s (A = OTf$^-$) and substrate/s ($S$ = Me$_2$N$^+$) are presented in Figure S17. Those consider the orbital donor towards the orbital acceptor interactions, which are shown in the direction of the arrow.

![Diagram showing orbital interactions](image)

**Figure S17.** Host-guest interactions of 1 with Me$_2$NTOF in 1:1, 1:2 and 1:3 stoichiometries ($E^{1G}$ in kcal mol$^{-1}$).

The binding $E^{1G}$ (shown in red) involving the catalyst 1 with one and two Me$_2$NTOF guests are 30 and 35% stronger than in case of chloride (e.g. for the 1:1 complexes: $E^{1G,1:1} = 47.4$ vs. 33.0 kcal mol$^{-1}$), respectively. Thus, the ability of the catalyst 1 to recognize triflate seems more prominent if one neglects all the other effects than electronic contribution arising from NBO stabilization energies. Moreover, conversely to the case of chloride, in the 1:2(OTf) complex the interactions between the counterparts of the two Me$_2$NTOF guests (S1-A1 and S2-A2) and the guests with the catalyst 1 (C-S and C-A) are not "symmetric" (equally distributed), and show a non-cooperative nature ($2 E^{1G,1:1} \neq E^{1G,1:2}$: 2·47.4–(42.4+52.4) = $-0.05$ kcal mol$^{-1}$). The stabilization between catalyst and the 2nd guest ($E_{C-S2-A2} = 52.4$ kcal mol$^{-1}$) is stronger than with the 1st guest ($E_{C-S1-A1} = 42.4$ kcal mol$^{-1}$), which is also reflected in a small weakening of the $E$ of the 2nd guest in respect to the 1st guest molecule ($E_{S1} = 20.7$ vs. 20.0 kcal mol$^{-1}$). This observation might arise from an extra interaction between the two different counterparts of the 1st and 2nd guest ($E_{S1,A2}$, shown in magenta).

For the binding of the 3rd guest molecule (A3-S3), the interaction between the catalyst and each of the anions is significantly reduced respect to the 1:2 complex ($E_{C,A}$ from $-30$ to $-16$ kcal mol$^{-1}$), while additional stabilization between the counterparts of the different guests is again observed. In order to get a deeper understanding of the contribution of a particular hydrogen to the overall binding energy, the strength of the HB was calculated considering the HB stabilization energy ($\epsilon$) for the H atoms relevant for the anion-binding (H$_1$-H$_8$). This allows us to compare our calculations with the experimental $^1$H-NMR-titration data in more detail. Thus, the HB stabilization energy originated from a particular HB formed between the catalyst and the anion is recalled as:

$$\epsilon_n = \sum \Delta E_{(H\rightarrow L)(FP)}^{(\gamma)}$$

where the sum runs over all interactions that involve an orbital of the catalyst 1, a hydrogen (H$_n$), and a lone pair of the anion atom/s (Figure S18a). The $\epsilon$ of each HB for the most stable complexes with Cl$^-$ and OTF$^-$, are shown in Figure S18b. Next, the effect of the conformer distribution in acetone at 25 °C (NMR titration conditions) was included (Figure S18c). Finally, we compared the results with the experiments, i.e. determined 1:1 stoichiometry for chloride, in which the $\epsilon$ that corresponds to indistinguishable $^1$H-NMR signals are summed up. Normalized to H$_3$, the relative values of the HB stabilization energy ($\Delta \epsilon$) (with the model TMACl salt) and the chemical shift ($\Delta \delta$) for 1:1 stoichiometry and 1 equivalent of Cl$^-$ (with TBACl) are shown in Figure S18d.
Figure S18. Analysis of HB strengths by correlation of the HB stabilization energy (c) with the NMR chemical shift (δ). Although the fitting procedure that uses all four chemical shifts of the relevant implied H-atoms (H1,5; H2,6; H3,7; H4,8) from ¹H-NMR showed very good agreement between measured and calculated binding energies, the further deeper analysis using NBO stabilization energies shows that the individual chemical shift does not directly correlate with a particular NBO predicted HB strength calculated with NBO, and only a qualitative agreement was achieved. However, the observed differences are consistent with the fact that the δδ obtained in the NMR experiments include other effects than pure hydrogen bond interactions, such as e.g. concentration of the guest molecule. The analysis of the latter effect is shown in Figure S18e. At higher concentrations the δδ is clearly reduced for the central triazole hydrogens (H1 and H5) with respect to the outer triazole hydrogens (H3 and H7), while a less significant effect is also observed for H2 and H4. This trend brings the experimental and theoretical results closer since, according to the Le Chatelier’s principle, higher concentrations of the guest should shift the equilibrium towards the formation of the 1:1 complex, while in the calculations the latter is considered exclusively. Finally, the contribution of each hydrogen bond (HnB) within the 1:1(Cl) complex to the super-molecular BE was estimated taking into account the previously calculated BE and \( \sum \omega_i \varepsilon_i \) (Table S5). From the total stabilization, 49% (-1.6 kcal mol\(^{-1}\)) in terms of BE arises from the interaction of the hydrogen atoms of the outer triazoles (H3+7) with Cl\(^-\), and 33% (-1.0 kcal mol\(^{-1}\)) from the central triazoles (H1+5).

| Hn | Contribution to \( E^{HCB}\) (kcal mol\(^{-1}\)) | Contribution to \( \varepsilon_i \) (%) | \( \varepsilon_i \) (kcal mol\(^{-1}\)) |
|----|-----------------------------------|----------------|----------------|
| 1  | 4.39                             | 16.4           | -0.52         |
| 2  | 1.30                             | 4.9            | -0.15         |
| 3  | 6.84                             | 25.5           | -0.80         |
| 4  | 1.43                             | 5.3            | -0.17         |
| 5  | 4.49                             | 16.8           | -0.53         |
| 6  | 0.65                             | 2.4            | -0.08         |
| 7  | 6.40                             | 23.9           | -0.75         |
| 8  | 1.26                             | 4.7            | -0.15         |
| Sum| 26.77                            | 100.0          | -3.15         |
| 1+5| 8.88                             | 33.2           | -1.04         |
| 2+6| 1.95                             | 7.3            | -0.23         |
| 3+7| 13.24                            | 49.5           | -1.56         |
| 4+8| 2.69                             | 10.1           | -0.32         |
| Sum| 26.77                            | 100.0          | -3.15         |

\( a \) Notice that indexes \( i \) and \( n \) describe particular isomer and Hn, respectively. \( b \) Contribution determined in respect to \( E^{HCB} \) of the most stable 1:1 complex. \( c \) \( \Delta H_{BE} \) = \( \frac{\sum \omega_i \varepsilon_i}{E^{HCB}} \). Quantum Theory of Atoms in Molecules (QTAIM)\(^{[9]}\) was performed to qualitatively characterize the nature of the HBs. The electron density (\( \rho \)) and Laplacian of electron density (\( \nabla^2 \rho \)) in eight bond critical points (BCP) (corresponding to H1-H8) are shown in Figure
S19. The comparison of the C-H distance, \( \sum \omega_i \varepsilon_i \) (NBO), \( \rho \) and \( \nabla^2 \rho \) (QTAIM) confirms the nature and binding strength of HBs, previously determined with the NBO method.

3.4. Folding Mechanism and CD Spectra

*Ab initio* Born-Oppenheimer molecular dynamics (BOMD) simulations were performed employing the DFT-M062X functional and the def-SV(P) basis set.[19] To speed up the simulations we used the resolution of identity approximation[20] and time step of 40 a.u. of time (= 0.97 fs). Microcanonical (NVE) ensemble at room temperature (25 °C) with randomly distributed thermal internal energy to nuclear degrees of freedom was performed. To sample the folding process dynamically we run several *ab initio* BOMD simulations to track the geometrical changes of the catalyst 1 towards the 1:1(Cl\textsubscript{11}) complex formation. We started by aligning the chiral backbone of the most stable 1 and 1:1(Cl) structures (Figure S20a). Next, the H\textsubscript{1}–Cl–N(Me\textsubscript{4}) angle was modified to 180°, and finally the guest molecule translated along the Cl–N displacement vector (Cl–N bond) of 1 Å. This procedure gives more freedom to the catalyst 1, thus being less bias for the chloride anion recognition by any of the hydrogens starting at a minimum distance of 5.5 Å between the host 1 and the Me\textsubscript{4}NCl guest. Other translations at longer displacement vectors than 1 Å (i.e. 2, 3, 4 and 5 Å) were also explored (two trajectories for each), however, they led to very long distances of HBs (C–H–Cl) and thus to unrealistic simulation times. The changes of the key C–C(cyclohexyl)–N–C(triazole) dihedral angles (C\textsubscript{6}–N\textsubscript{5}–C\textsubscript{1}–C\textsubscript{2} and C\textsubscript{1}–C\textsubscript{2}–N\textsubscript{3}–C\textsubscript{4}) and the HBs distances for an exemplary trajectory are presented in Figure S20b and S20c/d, respectively. In the first 100 fs of the simulation, only the hydrogens H\textsubscript{1} and H\textsubscript{5} from the central triazoles interact with the chloride anion, while other C-H bonds do not contribute or even slightly increase their distance to Cl\textsuperscript{−}. At 400 fs, the chloride is well recognized by H\textsubscript{1} and H\textsubscript{5}. From here, a strong desymmetrization of the interactions of the two arms of the catalyst takes place. One arm of the catalyst 1 interacts stronger with the chloride anion ("binding arm", H\textsubscript{1}–H\textsubscript{4}), while the other ("non-binding arm", H\textsubscript{5}–H\textsubscript{8}) opens (increase of the dihedral angle) to lead space for the ammonium salt substrate. Consequently, all other H-atoms of the binding arm start to contribute to the anion binding by hydrogen bonding, and form a stable complex at around 700 fs. At 800 fs, the dihedral angle of the binding arm of 1 is almost as for the 1:1 complex, however, the angle increases again to facilitate the allocation of the substrate in the structure and turn of the other catalyst’s arm. Next, the dihedral angle drops again at 1700 fs, going towards the dihedrals (64/80°) of the 1:1 complex. However, the complete closing of both arms is most probably a long time-scale process and cannot be observed in the *ab initio* BOMD simulations.

![Figure S19](image-url) HB acceptor distance (H–Cl in Å) as a function of a) HB donor distance, b) HB stabilization energy, c) electron density at BCP, and d) Laplacian of electron density at BCP.
Circular dichroism

The CD spectra were calculated with Time-Dependent DFT\cite{21} using the 6-31G(d,p) basis set. Several tests were made to validate the results with respect to the chosen DFT functional (CAM-B3LYP\cite{22} vs. M062X), solvation model (CPCM, IEEPCM and SMD) and the number of the lowest electronically excited states (50 vs. 100). The sensitivity of this analysis is summarized in Figure S21.

The stoichiometries and conformations of the most stable structures of the catalyst 1 and its 1:1 and 1:2 complex with chloride in THF were analyzed by comparing the calculated and experimental CD spectra. For the 1:1(Cl) complex a qualitative agreement was found, for which a new characteristic peak, not present for the pure catalyst, appeared in both the experimental (λ = 250 nm) and the calculated CD spectra with the M062X functional and 100 electronically excited states (λ = 180 nm). Its rotatory strength is reduced for the CAM-B3LYP functional to R ≈ 50 10^-40 cgs, but it is still clearly seen for all solvation models. On the contrary,
there is no theoretical evidence of the contribution of the 1:2 complex to the recorded experimental CD spectra. Moreover, in order to achieve a better agreement with the experiments, it was necessary to include the Boltzmann factor ($\omega_i$) for flexible molecules like 1 (Figure S22). Therefore, additional single point energy calculation with COSMO-RS model at 25 °C for all isomers were run (Table S6).

![Figure S22](image)

**Figure S22.** a) Weighted (SMD model, M062X functional and 100 excited states) and b) experimental CD spectrum of 1.

| Conformer | $\Delta E^*$ | $\omega_i$ |
|-----------|--------------|------------|
| I         | 0.00         | 0.6124     |
| II        | 0.86         | 0.1435     |
| III       | 1.18         | 0.0832     |
| IV        | 1.34         | 0.0639     |
| V         | 1.76         | 0.0313     |
| VI        | 1.73         | 0.0331     |
| VII       | 2.29         | 0.0128     |
| VIII      | 2.55         | 0.0083     |
| IX        | 2.73         | 0.0061     |
| X         | 3.00         | 0.0039     |
| XI        | 3.56         | 0.0015     |

* Relative total energies in THF at 25 °C in kcal mol$^{-1}$.

### 3.5. Model Reaction

Three transition states (TSs) were found for the model Reissert reaction with a pyridinium salt (Figure S23). The structures of TS1 and TS3 show one interaction of the Cl$^-$ with the substrate (pyridinium) and the nucleophile (methyl-trimethylsilylketene acetal), and a multideterminate interaction with the catalyst, while for TS2 only a monodeterminate interaction between the catalyst and the substrate is observed.

![Figure S23](image)

**Figure S23.** Structures of the found TSs for the model Reissert reaction.

The relative total energies ($E_{\text{rel}}$) calculated for the transition states (TS1, TS2 and TS3) include the thermal correction, i.e. the contribution of enthalpy ($H_{\text{AM1}}^\text{calc}$) and entropy ($S_{\text{AM1}}^\text{calc}$) with the quasi-rigid-rotor-harmonic-oscillator approximation[13] and zero-point energy correction ($E_{\text{ZPE}}^\text{calc}$) at semi-empirical AM1 level.[23] Electronic ($E_{\text{SCF}}$) and solvation energies ($G_{\text{solv}}$) were computed at DFT level with the M06-2X and BP86 functionals, respectively, and the def2tzvp basis set. Intrinsic Reaction Coordinate (IRC) profiles were obtained at M06-2X//def2tzvp/AM1 level of theory, including the single point corrected electronic
DFT energy and the solvent effect of THF, Et₂O and toluene at -78 and 25 °C using COSMO-RS theory. Therefore, the $E_a$ is defined as:

$$E^{DFT/AM1} = G^{DFT/AM1} + G_{solv}$$

(10)

where Gibbs energy ($G$) is defined as:

$$G^{DFT/AM1} = E^{DFT} + E^{AM1}_{SCF} + E^{AM1}_{thermal}$$

(11)

and $E^{AM1}_{thermal}$ is:

$$E^{AM1}_{thermal} = H^{AM1} - (E^{AM1}_{SCF} + E^{AM1}_{ZPE}) - T S^{AM1}$$

(12)

The IRC profiles were next analyzed, showing the relative position of TSs and the changes of the slopes towards the substrate and product as disclosed in Figure S24a. Moreover, the free energy surface with thermal effects ($G^{AM1}_{thermal}$, see Eq.12) at -78 and 25 °C were further analyzed for the lowest-lying TS1 (Figure S24b, left). In addition, the effect of the solvent (THF and Et₂O) at 25 °C and -78 °C was calculated (Figure S24b; middle and right, respectively). Finally, free energy surfaces for three barriers (TS1, TS2 and TS3) and corresponding minima at -78 °C in various solvents (THF, Et₂O and toluene) verified by IRC calculations are shown in Figure S24c. Thus, the reaction pathway via TS1 is the most kinetically (lowest barrier) and thermodynamically favorable (the most stable product), while the TS2 leads to an adduct with a weakly bonded HCl molecule, and the TS3 (more open structure) to an intermediate almost equally stable as the substrate. The final TMSCI elimination step seems to be also the easiest for the intermediate obtained via TS1, presenting a short Si-Cl distance of 3.85 Å (vs. 5.95 Å and 6.24 Å for the intermediates from TS2 and TS3, respectively).

**Figure S24. TS analysis: a) IRC profiles, b) critical points on free energy surface (PES+effects) for TS1, and c) free energy surface for all three reaction pathways (relative energies in kcal mol⁻¹).**
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Author Contributions

D G. Piekarski carried out all computations and lead the computational work. The experimental, validation and analysis studies were conducted by P. Steinforth, M. Gómez-Martínez and J. Bamberger, who carried out the anion-binding and NL effect experiments; F. Ostler recorded and analyzed the CD Spectra. M. Schönhoff and O. García Mancheño coordinated the project. O. García Mancheño wrote the original draft, and all authors participate in finalizing the manuscript.