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Catalysis with Chalcogen Bonds

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Abstract: *Herein, we introduce catalysts that operate with chalcogen bonds. Compared to conventional hydrogen bonds, chalcogen bonds are similar in strength but more directional and hydrophobic, thus ideal for precision catalysis in apolar solvents. For the transfer hydrogenation of quinolines and imines, rate enhancements well beyond a factor of 1000 are obtained with chalcogen bonds. Better activities with deeper σ holes and wider bite angles, chloride inhibition and correlation with computed anion binding energies are consistent with operational chalcogen bonds. Comparable to classics, such as 2,2′-bipyrroles or 2,2′-bipyridines, dithieno[3,2-b;2′,3′-d]thiophenes (DTTs), particularly their diimides, but also wide-angle cyclopentadithiazole-4-ones are identified as privileged motifs to stabilize transition states in the focal point of the σ holes on their two co-facial endocyclic sulfur atoms.*

Chalcogen bonds originate from the "σ holes" in the σ* orbitals of the covalent bonds of electron-deficient sulfur, selenium, or tellurium but not oxygen atoms (Figure 1 a,b).[1–7] Sulfur atoms as chalcogen-bond donors are thus similar to hydrogen-bond donors, such as N–H (rather than hydrogen-bond acceptors, such as oxygen atoms). Compared to conventional hydrogen-bond donors, chalcogen-bond donors are more directional and more hydrophobic, characteristics which make them appear perfect for catalysis in apolar media. However, contrary to the related halogen bonds,[1,2,8,9] the σ holes are somewhat hidden on the side of the chalcogen atom, next to the second covalent bond (Figure 1 a,b). Perhaps because of this peculiar location, their use, particularly in medicinal chemistry and materials sciences, has so far mainly focused on intramolecular conformational control and solid-state crystal engineering.[1–3] Experimental evidence for anion binding in solution is rare and recent,[4] and anion transport with chalcogen bonds has just been realized.[5] Moreover, pioneering examples for intramolecular conformational control in covalent catalysis have been reported.[6] Herein, we introduce chalcogen bonds to intermolecular, non-covalent catalysis.

Dithieno[3,2-b;2′,3′-d]thiophenes (DTTs)[7] and related structures were considered as general motif for chalcogen bonding in functional systems (Figure 1 c) that complements classics, such as 2,2′-bipyrroles or 2,2′-bipyridines.[5] The central single-atom bridge D between the peripheral rings is conceived as important to increase the bite angle for optimal bidentate substrate binding in the focal point of the σ holes on the cofacial endocyclic chalcogens Ch (Figure 1 c).[5] In DTT **1**, this bridge D is a sulfone acceptor, and cyano acceptors are added in *ortho* position to further deepen the σ holes on the co-facial sulfurs (Figures 1 c–f, Figure 2 a). In density functional theory (DFT) calculations at the M062X/6-311G** level of theory,[5] carbonyl lone pairs were poorly recognized by these deep σ holes (Figure 1 e). Presumably because of mismatched geometries, only one lone pair seems to be bound in the tilted global minimum. The computed interaction energies were correspondingly weak (e.g. $E_{int} = -5.8$ kcal mol^{-1} for formaldehyde binding to DTT **1**). Better results were obtained for the single lone pair on endocyclic nitrogen atoms of aromatic heterocycles (e.g. $E_{int} = -8.1$ kcal mol^{-1} for pyridine binding to DTT **1**, Figure 1 d). Based on these predictions from theory, transfer hydrogenation of quinolines[9] was selected to initially explore the possibility to catalyze organic transformations with chalcogen bonds (Figure 2 b).

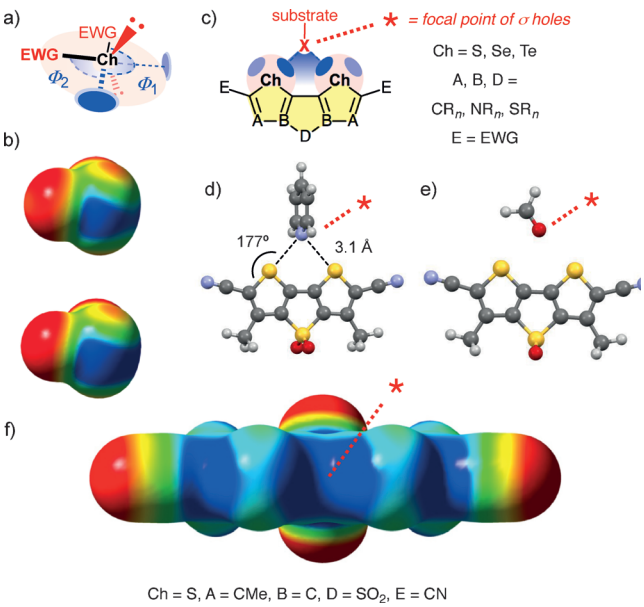

Figure 1. a) Location of σ holes (blue circles, $\Phi_1 \approx 180°$, $\Phi_2 \approx 70°$) on electron-deficient chalcogen (Ch) atoms (EWG: electron-withdrawing group). b) electrostatic potential surface (EPS) of SF_2 (top) and SeF_2 (bottom, blue: electron poor, red: electron rich).[2] c) General concept for substrate activation in the focal point of the two cofacial chalcogen-bond donors in DTTs (dithieno[3,2-b;2′,3′-d]thiophenes). d) Computed structure of the complex of DTT **1′** (see Figure 2, **1** with methyl instead of isobutyl substituents) with pyridine and e) formaldehyde. f) EPS of catalyst **1′** (MP2/6-311++G**//M062X/6-311G**, isosurface: 0.009 au; red: −0.012 au, blue: 0.07 au).[5]

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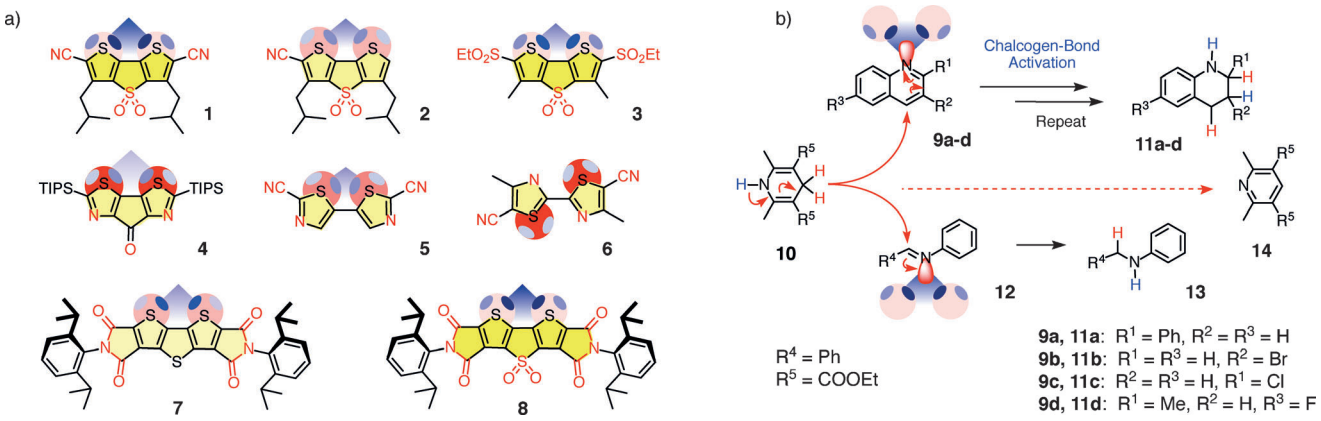

Figure 2. a) Structure of catalyst candidates **1**–**8** explored in this study to b) accelerate the transfer hydrogenation of quinolines **9** and imine **12**.

Catalysts **1**–**8** (Figure 2a) were envisioned to elaborate on chalcogen-bond catalysis. They were accessible in a few synthetic steps from commercially available starting materials following published methods.[5,10–12] Initial studies focused on DTTs **1**–**3** because of their proven ability to bind and transport anions in solution.[5] In the presence of 30 mol% **1**, the reduction of 2-phenyl quinoline **9a** with Hantzsch ester **10** afforded tetrahydroquinoline **11a** within 12 days at room temperature in 96% yield (Figure 3a, Table 1, entry 1). No

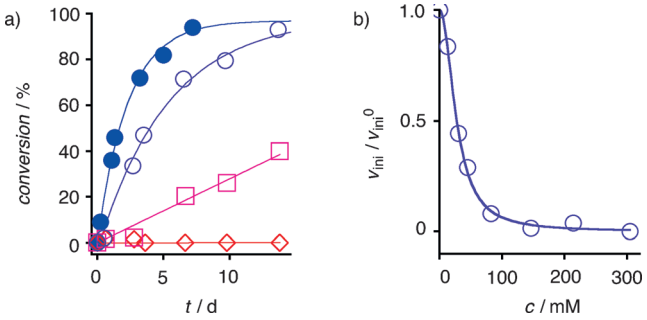

Figure 3. a) Formation of product **11a** with time in the presence of substrates **9a** and **10** and 0 mol% catalyst (◇) or 30 mol% catalysts **3** (□), **1** (○), and **8** (●). b) Initial velocity of the formation of product **11a** in the presence of **9a**, **10**, 30 mol% catalyst **1** and increasing concentrations of TBACl, with fit to Hill equation ($IC_{50} = 27 \pm 1$ mM).

turnover was observed under the same conditions without catalyst (Figure 3a, Table 1, entry 9). Only at higher substrate concentrations and after prolonged reaction time, trace amounts of product **11a** were formed. From the initial velocity of product formation, a $k_{uncat} = 3.9 \times 10^{-5}\,M^{-1}h^{-1}$ was obtained for transfer hydrogenation without catalyst. Comparison with the obtained $k_{cat} = 1.9 \times 10^{-2}\,M^{-1}h^{-1}$ revealed a rate enhancement of $k_{cat}/k_{uncat} = 490$ for catalyst **1** (Table 1, entry 1). This rate enhancement suggested that activation of the hydride acceptor by chalcogen bonding to catalyst **1** stabilized the transition state (and/or destabilized the substrate) by $\Delta\Delta G_{TS} = -15.3\,kJ\,mol^{-1}$ (Table 1, entry 1). Replacement of the cyano acceptors by sulfones in **3** and removal of one cyano acceptor in **2** reduced the catalytic activity 5 to 7 times, respectively (Table 1, entries 1–3).

Addition of TBACl to the reaction mixture caused the complete inhibition of catalyst **1** (Figure 3b). The $IC_{50} = 27 \pm 1$ mM obtained from the dose response curves was in the range of the previously found chloride binding in THF (Table S1).[5]

The good correlation between the catalytic activity and computed anion binding energies as well as inhibition with chloride provided experimental support for operational

Table 1: Characteristics of chalcogen-bond catalysts.[a]

Entry	Cat[b]	E_{int} [kcal mol^{-1}][c]	S[d]	η [%][e]	k_{cat}/k_{uncat}[f]	$\Delta\Delta G_{TS}$ [kJ mol^{-1}][g]
1	**1**	−34.6	**9a**	96	490	−15.3
2	**2**	−27.4	**9a**	81	67	−10.4
3	**3**	−32.7	**9a**	62	100	−11.4
4	**4**	−24.8	**9a**	82	125	−11.9
5	**5**	−26.9	**9a**	–[h]	–	–
6	**6**	−23.5	**9a**	–[h]	–	–
7	**7**	−28.3	**9a**	78	500	−15.3
8	**8**	−36.1	**9a**	94	1290	−17.7
9	–	–	**9a**	–[h]	–	–
10	**1**	−34.6	**9b**	97	4.0	−3.1
11	–	–	**9b**	–[h]	–	–
12	**1**	−34.6	**9c**	–[h]	–	–
13	**1**	−34.6	**9d**	–[h]	–	–
14	**1**	−34.6	**12**	95	50	−9.6
15	**2**	−27.4	**12**	85	3.9	−3.4
16	**3**	−32.7	**12**	72	6.6	−4.6
17	**4**	−24.8	**12**	99	5.6	−4.3
18	**5**	−26.9	**12**	–[h]	2.1	−1.8
19	**6**	−23.5	**12**	–[h]	1.8	−1.4
20	**7**	−28.3	**12**	85	190	−13.0
21	**8**	−36.1	**12**	95	335	−14.3
22	–	–	**12**	–[h]	–	–

[a] Reactions were conducted in CD_2Cl_2 at 20°C with **10** (entries 1–13: 281 mM; entries 14–22: 375 mM), catalyst **1**–**8** (entries 1–8, 10, 12 and 13: 30 mol%; entries 14–21: 10 mol%) and substrates **9** (entries 1–13: 128 mM) or **12** (entries 14–22: 250 mM), and monitored by ^{1}H NMR spectroscopy. [b] Catalysts, see Figure 2a. [c] Binding energies with chloride in the gas phase, calculated with M062X/6–311G**, data for **1**–**3** are from Ref. [5]. [d] Substrates, see Figure 2b. [e] Yield of the reduced product, determined by ^{1}H NMR integration. [f] Rate enhancement, k_{uncat} (**9a**) $= 3.9 \times 10^{-5}\,M^{-1}h^{-1}$, k_{uncat} (**9b**) $= 0.19\,M^{-1}h^{-1}$, k_{uncat} (**12**) $= 1.5 \times 10^{-3}\,M^{-1}h^{-1}$. [g] Transition-state stabilization (or ground-state destabilization), $k_{cat}/k_{uncat} = \exp(-\Delta\Delta G_{TS}/RT)$. [h] Not determined, very slow conversion.

chalcogen bonds in intermolecular catalysis. Quinolines **9b**–**9d** were reduced in the presence of catalyst **1** as well (Table 1, entries 10–13). Quinoline **9b** was the most reactive substrate and yielded the product **10b** in 97% yield within 8 h, whereas the reduction of quinolines **9c** and **9d** was much slower.

In the presence of 10 mol% catalyst **1**, the reduction of the more reactive imine **12** afforded amine **13** in 95% yield (Table 1, entry 14, Figure 2b). Compared to the uncatalyzed background reaction (Table 1, entry 22), the rate enhancement calculated to $k_{cat}/k_{uncat} = 50$. In support of operational chalcogen bonds, decreasing depth of the σ holes in catalysts **3** and **2** reduced the rate enhancement to $k_{cat}/k_{uncat} = 6.6$ and $k_{cat}/k_{uncat} = 3.9$, respectively (Table 1, entries 15 and 16). Compared to quinoline reduction, transition-state stabilizations were smaller for this transformation, presumably because the nitrogen lone pair in imine **12** is less accessible and less basic.

The weakest catalyst of the series was 5,5′-dicyano-2,2′-bi-1,3-thiazole **6** (Figure 2). A rate enhancement of $k_{cat}/k_{uncat} = 1.8$ was found for the reduction of imine **12** (Table 1, entry 19). The structural motif was of interest also because it is present in the light emitting oxyluciferin that accounts for the bioluminescence of fireflies, and in several macrocyclic natural products.[1] The negligible catalytic activity found for **6** reflected potent self-inhibition expected from intramolecular 1,4 S–N chalcogen bonds (Figure 2a).[1,2] Attempts to increase catalytic activity by additional cation binding to lock the two nitrogen atoms on one side were so far not successful. However, almost as poor activity found for 5,5′-bithiazole **5** indicated that a correct bite angle for transition-state stabilization in the focal point of the two σ holes is presumably even more important ($k_{cat}/k_{uncat} = 2.1$, Table 1, entry 18; Figure 1d, Figure 2). Indeed, the ultralarge bite angle with a tight carbonyl bridge in the cyclopenta[2,1-*b*;3,4-*b*′]dithiazole-4-one **4** increased catalytic activity with regard to imine reduction significantly, despite the absence of strongly withdrawing cyano acceptors ($k_{cat}/k_{uncat} = 5.6$, Table 1, entry 17). Quinoline reduction with the carbonyl-bridged catalyst **4** was with $k_{cat}/k_{uncat} = 125$ even better than with the DTT catalysts **2** and **3** but remained about 4-times inferior to the most powerful catalyst **1** (Table 1, entries 1–4). Intermolecular chalcogen bonding between sulfur and oxygen has been observed previously for this intriguing wide-angle motif **4** in the solid state.[10]

DTT diimides or "DDIs" **7** and **8** were synthesized[5,11,12] to increase catalytic activity beyond DTT **1** (Figure 2). Consistent with computational predictions in the gas phase ($E_{int} = -36.1$ kcal mol^{-1}, Table 1) and fluorescence measurements for 1:1 chloride binding in solution ($K_D = 950 \pm 50$ μM, Figure S5, Table S1), DDI **8** accelerated the transfer hydrogenation of quinoline **9a** more than a thousand times ($k_{cat}/k_{uncat} = 1290$, Table 1 entry 8). The rate enhancement $k_{cat}/k_{uncat} = 335$ for the reduction of imine **12** identified DDI **8** was more than 6 times above the previous best, that is, dicyano DTT **1** (Table 1, entries 21, 14).

The less-activated DDI **7** with "sulfide" instead of "sulfone" bridges between the two thiophenes remained remarkably active with regard to both quinoline ($k_{cat}/k_{uncat} = 500$) and imine reduction ($k_{cat}/k_{uncat} = 190$, Table 1, entries 7, 20), possibly because of additional contributions from anion-π catalysis.[13] This interpretation was supported by the higher activity of the expanded DDI **7** to reduce the planar imine **12** (more active than **1**) than the twisted 2-phenyl quinoline **9a** (as active as **1**).

Taken together, these results provide compelling direct experimental evidence for existence and significance of intermolecular chalcogen bonds in catalysis. Dithieno[3,2-b;2′,3′-d]thiophenes (DTTs), particularly their diimides, but also wide-angle cyclopentadithiazole-4-ones are thus confirmed as privileged motifs to integrate chalcogen bonds into functional systems in the broadest sense.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: chalcogen bonds · dithienothiophenes · homogeneous catalysis · transfer hydrogenation

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Communications

Homogeneous Catalysis

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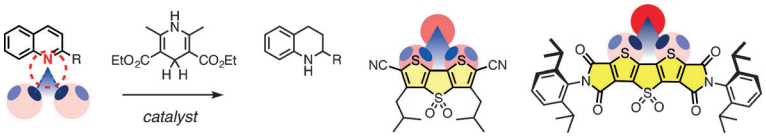

In the focal point: The integration of chalcogen bonds into non-covalent catalytic systems is realized with deep σ holes and wide bite angles between cofacial endocyclic sulfur atoms of dithieno[3,2-b;2′,3′-d]thiophenes (DTTs), ready to activate hydride acceptors for transfer hydrogenation of quinolines and imines by lone-pair recognition in the transition state.