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COMMUNICATION

Chalcogen-Bonding Catalysis: From Neutral to Cationic Benzodiselenazole Scaffolds

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Benzodiselenazoles (BDS) are emerging as privileged structures for chalcogen-bonding catalysis in the focal point of conformationally immobilized σ holes on strong selenium donors in a neutral scaffold. Whereas much attention has been devoted to work out the advantages of selenium compared to the less polarizable sulfur donors, high expectations concerning bidentate, rigid, and neutral scaffolds have been generated with little experimental support. Here we report design, synthesis and evaluation of the necessary catalysts to confirm that i) bidentate BDS are more effective than their monodentate analogs, ii) conformationally immobilized scaffolds are more effective than more flexible ones, iii) cationic BDS scaffolds are more effective than neutral ones, and iv) in dicationic-bidentate BDS, contributions from chalcogen-bonding dominate possible contributions from ion-pairing catalysis. These conclusions result from rate enhancements found for a *Ritter*-type anion-binding reaction and an X-ray crystal structure of dicationic BDS with a triflate anion bound with highest precision in the focal point of the σ holes.

Keywords: chalcogens, chalcogen-bonding catalysis, supramolecular chemistry, unorthodox interactions, selenium-containing heterocycles, heterocycles.

Introduction

The integration of new interactions into functional systems is of general interest, because it promises access to new structures with new functions.[1][2] This focus on unorthodox interactions at work accounts for the recent discovery of catalysis with anion-π interactions,[3] halogen bonds,[2] chalcogen bonds,[4] and pnictogen bonds,[5] and the renewed attention to their conventional counterparts such as cation-π interactions.[6] The large, polarizable, almost directionless π surface offered by anion-π interactions appears ideal to stabilize anionic transition states that involve charge displacements over longer distances, *e.g.*, cascade cyclizations.[7 – 9] The advantages of σ-hole interactions,[10 – 13] the unorthodox counterpart of hydrogen bonds, appear almost complementary: More hydrophobic and directional than hydrogen bonds, they should be ideal for high-precision catalysis in apolar media.

Originating from anti-bonding σ^* orbitals, chalcogen bonds extend linearly from the covalent bonds (bond angle $\Phi_1 \sim 180°$) and thus appear on the side of the chalcogen atom (bond angle $\Phi_2 \sim 70°$, *Figure 1,a*).[10 – 13] They have been studied extensively in crystal engineering and for intramolecular conformational control in solution, including prominent use in medicinal chemistry and pioneering applications in covalent catalysis.[11 – 17] The use of intermolecular chalcogen bonds in functional systems in solution is rare and recent,[13 – 22] non-covalent chalcogen-bonding catalysis has been introduced only last year.[4][23][24] The key to success was the idea that the somewhat awkwardly 'hidden' position of the σ holes on the side of chalcogen-bond donors turns into an advantage as soon as transition-state recognition in the focal point of two adjacent donors is considered.[4] Dithiophenes (*Figure 1,d*) were taken as starting point to think about chalcogen-bonding scaffolds for the recognition of electron-rich motifs in ground and transition state that would reflect the fundamental general versatility of classics such as metal-binding bipyridines (*Figure 1,b*) or hydrogen-bonding bipyrroles (*Figure 1,c*). However, in dithiophenes, the bite angle $\Phi_3 = 34°$ was too small for binding in the focal point of the σ holes (*Figure 1,d*). This bite angle was adjusted to $\Phi_3 = 45°$ by adding a single-atom sulfur bridge between the two

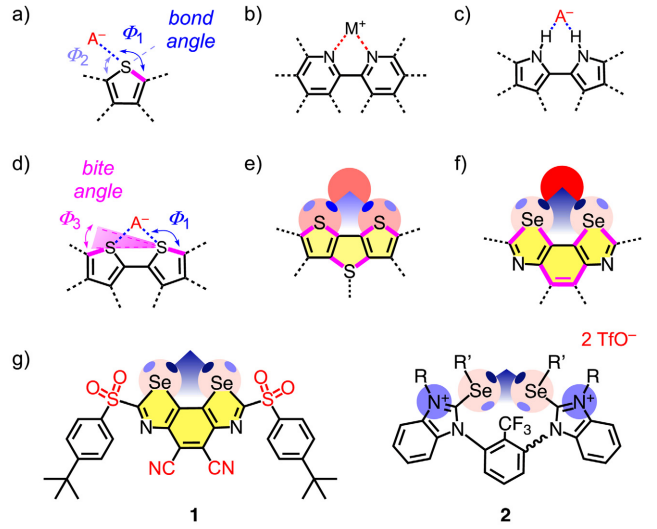
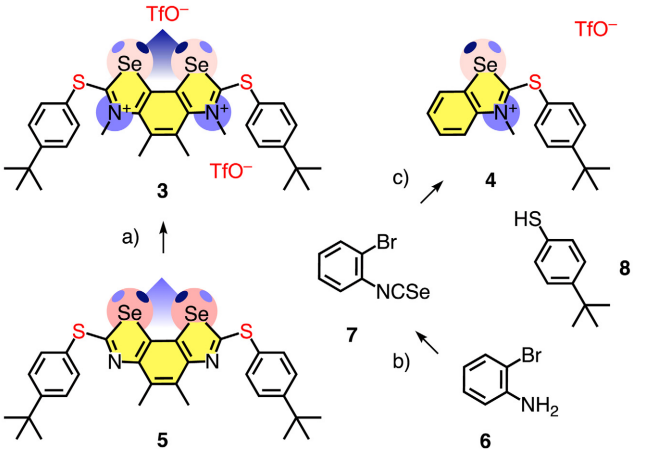


Figure 1. Concept and evolution of chalcogen-bonding catalysis. *a*) Schematic anion binding to thiophenes, with ideal bond angles $\Phi_1 \sim 180°$ and $\Phi_2 \sim 70°$. *b*) Cation binding by 2,2′-bipyridines. *c*) 2,2′-Bipyrroles with hydrogen-bonded anions. *d*) 2,2′-Dithiophenes ($\Phi_3 = 34°$, $\Phi_1 = 149°$), *e*) DTTs ($\Phi_3 = 45°$, $\Phi_1 \sim 180°$), and *f*) BDS ($\Phi_3 = 45°$, $\Phi_1 \sim 180°$) with chalcogen-bonded anions. *g*) Previously reported chalcogen-bonding catalysts.[23][24]

heterocycles. The result were dithieno[3,2-*b*:2′,3′-*d*]thiophenes (DTTs) with an ideal $\Phi_3 = 45°$ (*Figure 1, e*).[4] However, the formal substitution of the sulfur donors in DTTs with stronger selenium donors again turned the bite angle out of focus, this time becoming too large ($\Phi_3 = 53°$) because of the long C–Se bonds. This mismatch was corrected to $\Phi_3 = 45°$ by replacing the single-atom bridge in DTTs with a double-atom bridge in benzo[1,2-*d*:4,3-*d*′]di([1,3]selenazole)s (BDS, *Figure 1,f*).[24]

BDS are a new motif. However, benzomonoselenazoles (BMS) have been explored previously with regard to their optoelectronic properties and possible applications in the materials sciences.[25][26] In the most active chalcogen-bonding BDS catalyst reported so far, *i.e.* **1**, the BDS scaffold is decorated with electron-withdrawing cyano and sulfone acceptors to deepen the σ holes on the endocyclic Se donors (*Figure 1,g*).[24] The superiority of selenium compared to the less polarizable sulfur donors for chalcogen-bonding catalysis has been clearly demonstrated.[24] However, the functional relevance of other characteristics of the BDS scaffold, that is i) bidentate binding in the focal point of proximal σ holes, ii) conformational rigidity, and iii) the possibility to easily inject positive charges into the selenazole heterocycles by methylation, has never been clarified experimentally. With regard to cationic chalcogen-bond donors, conformationally more flexible chalcogen-bonding



Scheme 1. Structure and schematic synthesis of cationic chalcogen-bonding catalysts. *a*) MeOTf, DCE, μW, 100 °C, 8 h, 90%. *b*) 1. $HCOOH/Ac_2O$, 40 °C, 1 h; 2. **6**, 0 °C to r.t., 1 h, quant.; 3. Et_3N, $POCl_3$, THF, r.t., 4 h, 63%; 4. Se, Et_3N, $CHCl_3$, reflux, 14 h, 63%. *c*) 1. NaH, THF, 0 °C, 30 min, quant.; 2. CuI, 1,10-phenanthroline, Cs_2CO_3, DME, reflux, 2 h, 91%; 3. MeOTf, DCE, 50 °C, 2 h, 74%.

bis(2-selanylbenzimidazolium) (SBI) catalysts **2** have been reported last year by the *Huber* group (*Figure 1,g*).[23] Cationic chalcogen-bond donors are intriguing because access to deepened σ holes comes at the cost of possible complications from competitive ion pairing, interference from counterions, and poor solubility.[27] In this short communication, we report design, synthesis and evaluation of the catalysts **3** and **4** that were needed to clarify these open questions (*Scheme 1*).

The dicationic-bidentate BDS catalyst **3** was obtained in 90% yield by methylation of the previously reported[24] BDS catalyst **5** with MeOTf (*Scheme 1*). Relatively harsh conditions, *i.e.*, microwave irradiation at 100 °C for eight hours, were needed because methylation required deplanarization of the peripherally crowded BDS backbone (*vide infra*). The monodentate-cationic BMS counterpart **4** was synthesized from 2-bromoaniline **6** in six steps, with a copper-catalyzed cascade cyclization of isoselenocyanate **7** with thiophenol **8** as the key transformation (*Schemes 1, S1*).

The activity of catalysts **1**, **3**, and **4** was assessed with the *Ritter*-type solvolysis of benzhydryl bromide **9** that was previously used by the *Huber* group to characterize catalyst **2** (*Figure 2*).[23] This reaction is well suited to test cationic catalysts, since it is acid insensitive and therefore only marginally affected by the possible presence of residual traces of acids from the counterion, *e.g.* HOTf.[23] Chalcogen-bonding catalysis of the solvolysis of benzhydryl bromide **9** in acetonitrile operates by transition-state recognition of the rate-limiting elimination of bromide. Reaction of

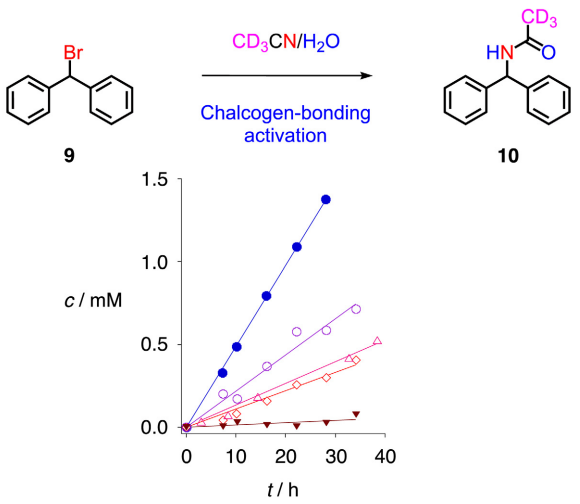


Figure 2. Initial velocity of the solvolysis of benzhyrdyl bromide **9** (16.5 mM) by wet (~1.6 equiv. H_2O), deuterated acetonitrile in the presence of chalcogen-bond activators **4** (1 equiv., ◇; 2 equiv., △), **3** (●), **1** (○) and without activator (▼), at room temperature.

the resulting carbocation with acetonitrile and hydrolysis of the nitrilium intermediate by traces of water in the solvent affords the *N*-benzhydryl acetamide **10**. In this reaction, chalcogen-bonding catalysts are used in stoichiometric amounts because of their possible inactivation by the eliminated bromide anion and thus act formally as activators rather than as catalysts. However, the previously confirmed function of **1** and **5** to catalyze transfer hydrogenation of quinolines and imines justifies the use of the term catalyst.[24]

Rate enhancements by chalcogen-bonding catalysts were determined based on molecular concentrations, independent of the number of chalcogen-bond donors per molecule. Following the standard *Huber* protocol,[23] linear fitting of the initial rate of product formation revealed a rate enhancement k_{cat}/k_{uncat} = 36 for the dicationic-bidentate BDS activator **3** (*Figure 2*, ● *vs.* ▼). This rate enhancement exceeded the k_{cat}/k_{uncat} = 8 and k_{cat}/k_{uncat} = 10 measured with one and two equivalents of the cationic-monodentate BMS activator **4**, respectively (*Figure 2*, ◇△). The bidentate-neutral BDS activator **1** was with k_{cat}/k_{uncat} = 17 (*Figure 2*, ○) more active than the cationic-monodentate BMS activator **4** (*Figure 2*, ◇), but clearly less active than the dicationic-bidentate BDS activator **3**, despite the presence of withdrawing cyano and sulfone acceptors (*Figure 2*, ●). In other words, deepening of the σ holes in the essentially inactive[24] precursor **5** with the four electron-withdrawing substituents in **1** (k_{cat}/k_{uncat} = 17) is less effective than with the two endocyclic positive charges in **3** (k_{cat}/k_{uncat} = 36).

Under identical conditions, k_{cat}/k_{uncat} = 34 has been reported for the *syn* atropisomer of the bidentate SBI activator **2**.[23] With k_{cat}/k_{uncat} = 23, the monodentate *anti* atropisomer of **2** was less active. In comparison, the monodentate *anti* SBI **2** was clearly more active than monodentate BMS activator **4** (k_{cat}/k_{uncat} = 23 *vs.* 10), whereas bidentate *syn* SBI **2** was slightly less active than bidentate DBS **3** (k_{cat}/k_{uncat} = 36 *vs.* 34).[23] This higher relative increase in activity from monodentate to bidentate benzoselenazole compared to SBI scaffolds supported the importance of conformational immobilization of the σ holes to maximize transition-state stabilization in their precisely localized focal point.

The central challenge with cationic chalcogen-bonding catalysts besides the presence of counterions are possible contributions from ion-pairing catalysis. In the present example, the bromide leaving group in substrate **9** could be activated next to one of the cationic nitrogens in **3** rather than in the focal point of the chalcogen-bond donors. The crystal structure[1] of catalyst **3** suggested that these concerns are not justified (*Figure 3*). One of the triflate anions was found in the focal point of the σ holes, with chalcogen bonds that excel with short bonds of maximal 2.90 Å and nearly ideal bond angles of minimal 167.8°. In the crystal structure, only the second triflate ion paired with one of the cationic nitrogens (not shown). Both aryl sulfides are in *syn* conformation with respect to the selenium donors, without contact to the anion. Peripheral crowding forces the methyl groups out of plane. To minimize contact, they naturally prefer an all-*trans* conformation. This deplanarization explained the harsh conditions needed for methylation of the neutral precursor **5**.

In summary, we conclude that in chalcogen-bonding catalysts with comparable selenium donors, dicationic-bidentate are better than neutral-bidentate scaffolds, neutral-bidentate are better than cationic-monodentate scaffolds, chalcogen-bonding

[1]Crystallographic data for **3** have been deposited with the *Cambridge Crystallographic Data Centre* as supplementary publication number CCDC-1846776. These data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting *The Cambridge Crystallographic Data Centre*, 12 Union Road, Cambridge CB2 1EZ, UK; fax: 441223 336033.

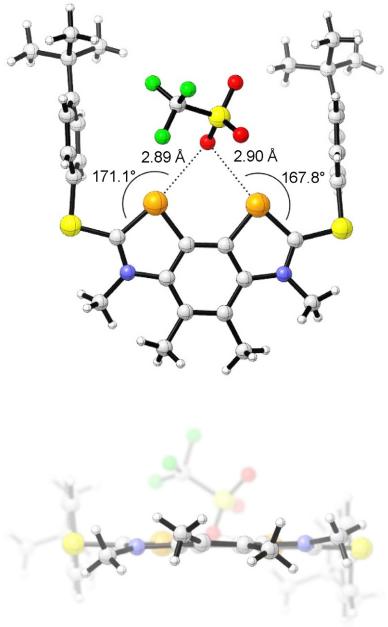


Figure 3. Top view of the X-ray crystal structure of **3** with relevant bond angles and distances. Solvent molecules and second counter anion have been omitted for clarity (Se, orange; O, red; S, yellow; F, green; N, blue; C, grey; H, white). The side view is shown below, highlighting the methyl groups forced out of the aromatic plane by peripheral crowding.

catalysis outperforms ion-pairing catalysis, and conformational immobilization of the σ holes for transition-state stabilization in their focal point is beneficial. These concise guidelines should be helpful for the future development of chalcogen-bonding catalysis.

Supplementary Material

Supporting information for this article is available on the WWW under https://doi.org/10.1002/hlca.201800075.

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Author Contribution Statement

S. B. and *S. M.* conceived this work, designed the experiments, discussed the results, and wrote the manuscript. *S. B.* synthesized and evaluated the catalysts, *C. B.* solved the crystal structure.

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