

Anion Transport with Chalcogen Bonds

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S Supporting Information

ABSTRACT: In this report, we introduce synthetic anion transporters that operate with chalcogen bonds. Electron-deficient dithieno[3,2-*b*;2',3'-*d*]thiophenes (DTTs) are identified as ideal to bind anions in the focal point of the σ holes on the cofacial endocyclic sulfur atoms. Anion binding in solution and anion transport across lipid bilayers are found to increase with the depth of the σ holes of the DTT anionophores. These results introduce DTTs and related architectures as a privileged motif to engineer chalcogen bonds into functional systems, complementary in scope to classics such as 2,2'-bipyroles or 2,2'-bipyridines that operate with hydrogen bonds and lone pairs, respectively.

Synthetic transport systems^{1–3} have emerged as an attractive tool to elaborate on the functional relevance of interactions that are otherwise less recognized.³ Leading examples for such unorthodox interactions at work in lipid bilayer membranes include halogen bonds and anion- π interactions.³ Here, we report the first example for anion transport with chalcogen bonds.

Chalcogen bonds originate from σ holes on electron-deficient sulfur, selenium, or tellurium but not oxygen atoms (Figure 1A).^{4–6} With the σ^* orbitals of the two C–X bonds accounting for the σ holes, chalcogen bonds extend colinear to these bonds, i.e., $\phi_1 \approx 180^\circ$. The resulting angle between a chalcogen bond and the other, coplanar C–X bond is, with $\phi_2 \approx 70^\circ$, relatively small. It is perhaps this small ϕ_2 that has limited the use of chalcogen bonds in functional systems mostly to intramolecular conformational control and solid-state crystal engineering.^{4,5} Anion binding with telluradiazoles in solution has been realized recently.⁶

2,2'-Bithiophenes⁷ were considered as a conceptually innovative motif for the design of chalcogen-bond transporters and beyond (Figures 1B). On the one hand, they are nicely complementary to 2,2'-bipyridines, the classical motif to bind cations rather than anions with the two nitrogen lone pairs (Figure 1C).⁸ On the other hand, they complement 2,2'-bipyroles (Figure 1D). This classical motif to bind anions with conventional hydrogen rather than unorthodox chalcogen bonds is present also in biological anion transporters such as prodigiosin and synthetic mimics in many variations.²

Density functional theory (DFT) modeling at the M062X/6-311G** level of theory^{9–11} in the gas phase supported 2,2'-bithiophenes as operational anionophores. Dithieno[3,2-*b*;2',3'-*d*]thiophenes (DTTs)^{5,12–14} appeared particularly attractive because the orientation of the cofacial σ holes is preorganized, and their bite angle is enlarged. The chalcogen-bond angle in

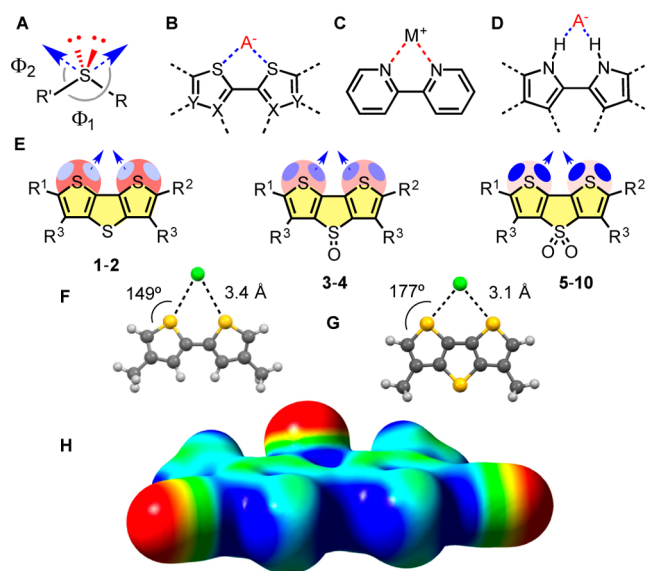


Figure 1. Design of chalcogen-bond anionophores. (A) Directionality of chalcogen bonds (dashed arrows) of sulfur atoms: $\Phi_1 \approx 180^\circ$, $\Phi_2 \approx 70^\circ$. (B–D) Envisioned anion complexes with 2,2'-bithiophenes (B) compared to classical complexes with 2,2'-bipyridines (C) and 2,2'-bipyroles (D). (E) Structure of the new transporters 1–10 (compare Table 1). (F–G) M062X/6-311G** optimized structures of chloride complexes of 2,2'-bithiophenes (F) and DTT 1 (G). (H) Electrostatic potential surface (EPS) computed at the MP2/6-311+G**//M062X/6-311G** level of theory for DTT 7 ($R^3 = \text{Me}$, blue: electron poor, red: electron rich).¹¹

chloride complexes was found to increase correspondingly from $\phi_1 = 149^\circ$ in 2,2'-bithiophenes (Figure 1F) to $\phi_1 = 177^\circ$ in DTT 1 (Figure 1F, G). The S–Cl distances decreased correspondingly to end up far below the sum of the van der Waals radii (3.7 Å; Figure 1F, G). Computed anion binding energies in 1:1 complexes increased with the depth of the σ holes, achieved by oxidation of the bridging “sulfide donors” in DTT 1–2 to “sulfoxides” in DTT-S-oxides 3–4 and “sulfone” acceptors in DTT-S,S-dioxides 5–10 (Figure 1E, Table 1).^{5,12–16} DFT models confirmed that one or two vicinal acceptors can further increase anion binding (e.g., 5–7, Table 1, Figure 1H; 7: $\phi_1 = 179^\circ$, S–Cl = 2.9 Å). The addition of heteroatoms in the thiophene ring produced deep σ holes together with strong computed binding. However, all bithiazoles tested were inactive as anion transporters, presumably because they are too hydrophilic to partition into

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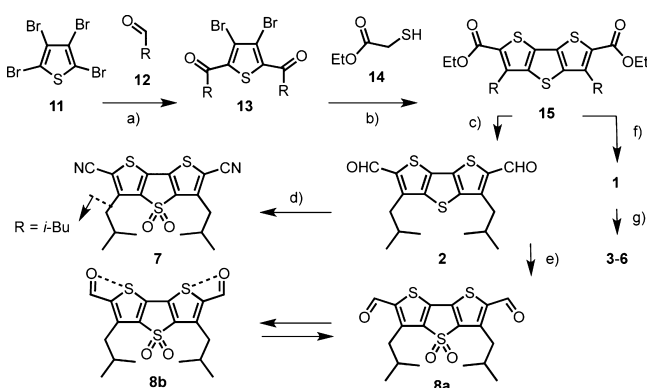
Table 1. Anion Binding and Transport with Chalcogen Bonds

comps ^a	bridge	R ¹	R ²	R ³	E_{int} (kcal mol ⁻¹) ^b	EC_{50} (μM) ^c	n^d	Cl ⁻ /NO ₃ ^{-e}
1	S	H	H	<i>i</i> -Bu	-9.9	16 ± 3	1.3	-
2	S	CHO	CHO	<i>i</i> -Bu	-21.3 (-14.7) ^f	- ^g	-	-
3	SO	H	H	<i>i</i> -Bu	-16.6	19 ± 2	1.1	3.4
4	SO	CN	H	<i>i</i> -Bu	-24.0	22 ± 4	1.2	2.3
5	SO ₂	H	H	<i>i</i> -Bu	-20.1	9.4 ± 0.6	1.5	2.2
6	SO ₂	CN	H	<i>i</i> -Bu	-27.4	7 ± 2	1.4	2.0
7	SO ₂	CN	CN	<i>i</i> -Bu	-34.6	1.9 ± 0.2	1.2	2.1
8	SO ₂	CHO	CHO	<i>i</i> -Bu	-30.9 (-24.8) ^f	- ^g	-	-
9	SO ₂	SO ₂ Et	H	Me	-26.8	27 ± 2	1.4	1.2
10	SO ₂	SO ₂ Et	SO ₂ Et	Me	-32.7	- ^g	-	-

^aSee Figure 1E for structures; bridge: Atoms bridging the two peripheral thiophenes in [3,2-*b*;2',3'-*d*]-DTTs. ^bInteraction energies for 1:1 chloride complexes computed at the M062X/6-311G** level and BSSE corrected; R³ = Me. ^cEffective concentration needed to reach 50% of maximal transport activity Y_{max} in the HPTS assay. ^dHill coefficient of dose response curves in the HPTS assay. ^eTransport activity in the HPTS assay with extravesicular chloride compared to extravesicular nitrate. ^fValue in parentheses for conformer **b** with competing intramolecular chalcogen bonds (Scheme 1). ^gNot detectable (fluorescence overlap, precipitation).

the membranes, and were thus not further investigated (not shown).

DTTs 1–10 were easily accessible by adapting previously reported synthetic procedures (Scheme 1).^{13,14} All details on DTT synthesis can be found in the Supporting Information (SI) (Schemes S1–S3).¹⁷

Scheme 1^a

^a(a) (1) BuLi, THF, -78 °C, 2 h, 69%; (2) Na₂Cr₂O₇, H₂SO₄, H₂O, acetone, rt, 16 h, 68%; (b) EtONa, EtOH, reflux, 2 h, 86%; (c) (1) DIBAL-H, THF, -78 °C, 30 min, quant; (2) Dess-Martin periodinane, CH₂Cl₂, rt, 2 h, 71%; (d) (1) NaN₃, TFOH, CH₃CN, 50 °C, 1 h, 71%; (2) mCPBA, CHCl₃, rt, 3 h, 77%; (e) mCPBA, CHCl₃, rt, 3 h, 36%; (f) (1) LiOH, EtOH, reflux, 16 h, 95%; (2) Ag₂CO₃, AcOH, DMSO, 120 °C, 16 h, 73%; (g) several steps, see SI.¹⁷

The absorption spectra of DTT 7 in THF showed a maximum at $\lambda_{\text{abs}} = 376$ nm (Figure 2A). Chloride binding caused appreciable hypo- and bathochromism, whereas the emission at $\lambda_{\text{em}} = 444$ nm did not shift but was almost completely quenched (Figure 2B). Analysis of dose response isotherms for 1:1 complexes gave a $K_D = 1.13 \pm 0.03$ mM (Figures S1, S2, Table S1). The Job plot supported formation of a 1:1 complex (Figure S3). Consistent with anion recognition by operational chalcogen bonds, binding of nitrate (TBANO₃) was clearly weaker ($K_D = 6.2 \pm 0.4$ mM, selectivity Cl⁻/NO₃⁻ = 5.6, Figure S4, Table S1). Binding of PF₆⁻ was not detectable (Figure S5).

Compared to 7, chloride binding by 6 with only one cyano acceptor was clearly weaker ($K_D = 14.4 \pm 0.7$ mM). Anion binding by all DTTs with shallower σ holes was not detectable.

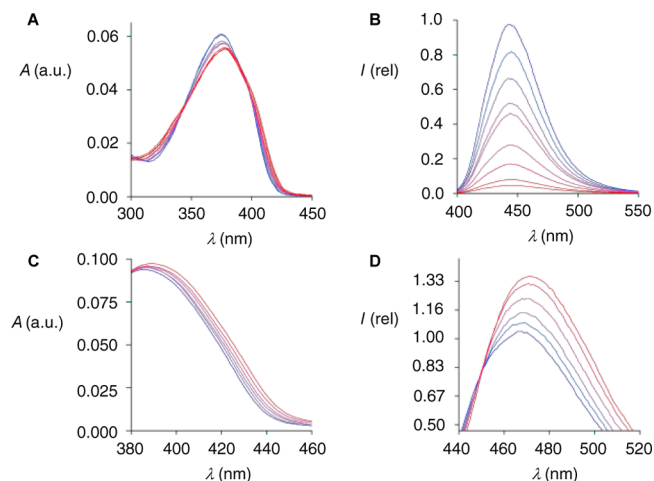


Figure 2. Absorption (A, C) and emission spectra (B, D, excitation at maxima) of 7 (A, B) and 8 (C, D) in THF in the presence of increasing concentrations of TBACl, from 0 mM (blue) to 20 mM (red).

Substitution of two cyano acceptors in 7 by sulfones in 10 did not significantly affect anion binding in THF ($K_D = 4.9 \pm 0.2$ mM, Cl⁻/NO₃⁻ = 2.6, Table S1). With two aldehyde acceptors in DTT 8, absorption ($\lambda_{\text{abs}} = 389$ nm) and emission ($\lambda_{\text{em}} = 472$ nm) increased with TBACl (Figure 2C, D). This hyperchromic response was consistent with competition from intramolecular chalcogen bonds in 8b (Scheme 1). The theoretically predicted decrease in chloride affinity of 8 (Table 1, entry 8) was confirmed experimentally ($K_D = 6.7 \pm 0.7$ mM).

Transport activities were assessed in large unilamellar vesicles (LUVs) composed of egg yolk phosphatidylcholine (EYPC) and loaded with 8-hydroxy-1,3,6-pyrenetrisulfonate (HPTS), a pH sensitive fluorescent probe.¹⁸ With a base pulse, a pH gradient was applied first, and then the transporters were added and their ability to accelerate the dissipation of the pH gradient was measured (Figures 3A, S6, S7). Activities were described by the effective concentration EC_{50} needed to reach 50% of the maximal activity Y_{max} (Figures S8, S9). For DTTs with methyl groups as substituents R³, transport activities were poor. With one sulfone acceptor in 9, $EC_{50} = 27 \pm 2$ μM could be measured (Table 1, entry 9); DTT 10 with two sulfones was inactive (Table 1, entry 10). With evidence for comparably strong anion binding in THF secured (above), undetectable

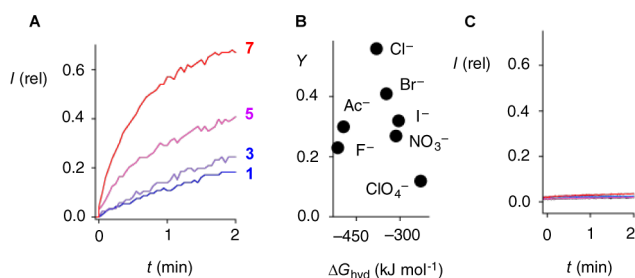


Figure 3. (A) Change in HPTS fluorescence ($\lambda_{\text{ex1}} = 400$ nm, $\lambda_{\text{ex2}} = 450$ nm) upon addition of 1, 3, 5, and 7 ($10 \mu\text{M}$) to EYPC LUVs with internal HPTS and a transmembrane pH gradient, calibrated to $I = 1.0$ after final lysis. (B) Dependence of transport activity Y of 7 on the nature of extravesicular anions (100 mM NaX, inside 100 mM NaCl). (C) Change in CF fluorescence ($\lambda_{\text{ex}} = 492$ nm) upon addition of 1, 3, 5, and 7 ($10 \mu\text{M}$) to EYPC LUVs with internal CF, calibrated to $I = 1.0$ after final lysis.

transport activity of DTT 10 was likely to originate from poor partitioning.

With isobutyl solubilizers as R^3 , DTTs 1–4 with weak σ holes delivered nondescript EC_{50} around $20 \mu\text{M}$ (Table 1, entries 1–4). With the most powerful “sulfone” bridges in 5–7, activities increased gradually with one and two additional cyano acceptors (Table 1, entries 5–7). The best $\text{EC}_{50} = 1.9 \pm 0.2 \mu\text{M}$ obtained for 7 coincided with the best $K_{\text{D}} = 1.13 \pm 0.03$ mM for chloride binding in THF and the highest theoretical binding energy $E_{\text{int}} = -34.6 \text{ kcal mol}^{-1}$, which is the deepest σ hole.

Hill coefficients were near $n = 1$ for all transporters (Table 1). Supported by curve fits and Job plots for anion binding in solution, this could suggest that DTTs transport anions as monomers.¹⁹ Consistent with anion-selective transport, presumably anion/ OH^- antiport,¹⁸ the exchange of extravesicular anions affected transport activities overall more than the exchange of external cations (Figures 3B, S10). The obtained apparent anion selectivity sequences should not be over-interpreted because of the complexity of the assay (results for Ac^- and F^- , for example, are influenced by passive diffusion of their conjugate acids, Figure 3B). The consistently moderate activity with external nitrate was noteworthy because transporters that operate with anion- π interactions show high activity with external nitrate (Figures 3B, Table 1).^{3,16,20} Relatively high LUMO energies down to $E_{\text{LUMO}} = -3.70$ eV obtained for DTT 7 from differential pulse voltammetry (DPV) firmly excluded any contributions for anion- π interactions to anion transport with chalcogen bonds (Figure S12; naphthalenediimide (NDI) anion- π transporters: $E_{\text{LUMO}} < -4.00$ eV, NDIs with -3.70 eV are π neutral^{3,21}). The electrostatic potential confirmed that the π surface of the tricyclic moiety is not suitable for anion- π interactions and that anion binding in the focal point of the σ holes on the proximal endocyclic sulfur atoms is clearly preferred (Figure 1H).

All new chalcogen-bond transporters were inactive in the CF assay (Figure 3C). These routine controls, operating on fluorescence recovery upon export of self-quenched 5(6)-carboxyfluorescein from CF-loaded EYPC LUVs,¹⁸ excluded that more significant membrane damage from detergent effects and the like account for the activity observed in the HPTS assay.

In summary, the reported results provide compelling experimental and theoretical evidence for the existence and significance of anion transporters that operate with chalcogen

bonds and introduce DTTs as a privileged motif to install chalcogen bonds in functional systems. Studies are ongoing to elaborate on these perspectives, particularly with regard to catalysis.¹⁶

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b05779.

Detailed experimental procedures (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) (a) Fyles, T. M. *Acc. Chem. Res.* **2013**, *46*, 2847–2855. (b) Otis, F.; Auger, M.; Voyer, N. *Acc. Chem. Res.* **2013**, *46*, 2934–2943. (c) Valkenier, H.; Davis, A. P. *Acc. Chem. Res.* **2013**, *46*, 2898–2909. (d) Gokel, G. W.; Negin, S. *Acc. Chem. Res.* **2013**, *46*, 2824–2833. (e) Montenegro, J.; Ghadiri, M. R.; Granja, J. R. *Acc. Chem. Res.* **2013**, *46*, 2955–2965. (f) Barboiu, M.; Gilles, A. *Acc. Chem. Res.* **2013**, *46*, 2814–2823. (g) De Riccardis, F.; Izzo, I.; Montesarchio, D.; Tecilla, P. *Acc. Chem. Res.* **2013**, *46*, 2781–2790. (h) Davis, J. T.; Okunola, O.; Quesada, R. *Chem. Soc. Rev.* **2010**, *39*, 3843–3862. (i) Satake, A.; Yamamura, M.; Oda, M.; Kobuke, Y. *J. Am. Chem. Soc.* **2008**, *130*, 6314–6315. (j) Jones, J. E.; Diemer, V.; Adam, C.; Raftery, J.; Ruscoe, R. E.; Sengel, J. T.; Wallace, M. I.; Bader, A.; Cockroft, S. L.; Clayden, J.; Webb, S. J. *J. Am. Chem. Soc.* **2016**, *138*, 688–695. (k) Huo, Y.; Zeng, H. *Acc. Chem. Res.* **2016**, *49*, 922–930. (l) Wei, X.; Zhang, G.; Shen, Y.; Zhong, Y.; Liu, R.; Yang, N.; Al-mkhaizim, F. Y.; Kline, M. A.; He, L.; Li, M.; Lu, Z.-L.; Shao, Z.; Gong, B. *J. Am. Chem. Soc.* **2016**, *138*, 2749–2754. (m) Si, W.; Xin, P.; Li, Z.-T.; Hou, J.-L. *Acc. Chem. Res.* **2015**, *48*, 1612–1619. (n) Muraoka, T.; Endo, T.; Tabata, K. V.; Noji, H.; Nagatoishi, S.; Tsumoto, K.; Li, R.; Kinbara, K. *J. Am. Chem. Soc.* **2014**, *136*, 15584–15595. (o) Saha, T.; Dasari, S.; Tewari, D.; Prathap, A.; Sureshan, K. M.; Bera, A. K.; Mukherjee, A.; Talukdar, P. *J. Am. Chem. Soc.* **2014**, *136*, 14128–14135.
- (2) Gale, P. A.; Busschaert, N.; Haynes, C. J. E.; Karagiannidis, L. E.; Kirby, I. L. *Chem. Soc. Rev.* **2014**, *43*, 205–241.
- (3) Vargas Jentzsch, A.; Hennig, A.; Mareda, J.; Matile, S. *Acc. Chem. Res.* **2013**, *46*, 2791–2800.
- (4) (a) Beno, B. R.; Yeung, K.-S.; Bartberger, M. D.; Pennington, L. D.; Meanwell, N. A. *J. Med. Chem.* **2015**, *58*, 4383–4438. (b) Bauzà, A.; Mooibroek, T. J.; Frontera, A. *ChemPhysChem* **2015**, *16*, 2496–2517. (c) Ho, P. C.; Szydłowski, P.; Sinclair, J.; Elder, P. J. W.; Kubel, J.; Gendy, C.; Lee, L. M.; Jenkins, H.; Britten, J. F.; Morim, D. R.; Vargas-Baca, I. *Nat. Commun.* **2016**, *7*, 11299. (d) Kremer, A.; Fermi, A.; Biot, N.; Wouters, J.; Bonifazi, D. *Chem. - Eur. J.* **2016**, *22*, 5665–5675. (e) Gsänger, M.; Kirchner, E.; Stolte, M.; Burschka, C.; Stepanenko, V.; Pflaum, J.; Würthner, F. *J. Am. Chem. Soc.* **2014**, *136*, 2351–2362.

(5) Getmanenko, Y. A.; Risko, C.; Tongwa, P.; Kim, E.-G.; Li, H.; Sandhu, B.; Timofeeva, T.; Bredas, J.-L.; Marder, S. R. *J. Org. Chem.* **2011**, *76*, 2660–2671.

(6) (a) Garrett, G. E.; Gibson, G. L.; Straus, R. N.; Seferos, D. S.; Taylor, M. S. *J. Am. Chem. Soc.* **2015**, *137*, 4126–4133. (b) Semenov, N. A.; Lonchakov, A. V.; Pushkarevsky, N. A.; Suturina, E. A.; Korolev, V. V.; Lork, E.; Vasiliev, V. G.; Konchenko, S. N.; Beckmann, J.; Griksan, N. P.; Zibarev, A. V. *Organometallics* **2014**, *33*, 4302–4314.

(7) Mishra, A.; Ma, C.-Q.; Bauerle, P. *Chem. Rev.* **2009**, *109*, 1141–1276.

(8) Kaes, C.; Katz, A.; Hosseini, M. W. *Chem. Rev.* **2000**, *100*, 3553–3590.

(9) Frisch, M. J. et al. *Gaussian 09*, Revision D.01; Gaussian, Inc.: Wallingford, CT, 2013. See SI for full citation.

(10) (a) Zhao, Y.; Truhlar, D. G. *J. Chem. Phys.* **2006**, *125*, 194101.

(b) Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215–241.

(11) (a) Dennington, R.; Keith, T.; Millam, J. *GaussView*, Version 5; Semichem Inc.: Shawnee Mission, KS, 2009. (b) Electrostatic potential is projected on the 0.009 au electron density isosurface, and its color coding ranges between -0.012 au (red) and 0.07 au (blue).

(12) (a) Cinar, M. E.; Ozturk, T. *Chem. Rev.* **2015**, *115*, 3036–3140.

(b) Barbarella, G.; Di Maria, F. *Acc. Chem. Res.* **2015**, *48*, 2230–2241.

(c) De Jong, F.; Janssen, M. J. *J. Org. Chem.* **1971**, *36*, 1645–1648.

(d) He, X.; Borau-Garcia, J.; Woo, A. Y. Y.; Trudel, S.; Baumgartner, T. *J. Am. Chem. Soc.* **2013**, *135*, 1137–1147.

(13) (a) Frey, J.; Bond, A. D.; Holmes, A. B. *Chem. Commun.* **2002**, *37*, 2424–2425. (b) Hong, W.; Yuan, H.; Li, H.; Yang, X.; Gao, X.; Zhu, D. *Org. Lett.* **2011**, *13*, 1410–1413.

(14) Veroleto, Q.; Rosspeintner, A.; Soleimanpour, S.; Sakai, N.; Vauthey, E.; Matile, S. *J. Am. Chem. Soc.* **2015**, *137*, 15644–15647.

(15) (a) Dado, G. P.; Gellman, S. H. *J. Am. Chem. Soc.* **1993**, *115*, 12609–12610. (b) Sakai, N.; Gerard, D.; Matile, S. *J. Am. Chem. Soc.* **2001**, *123*, 2517–2524.

(16) (a) Cotellet, Y.; Benz, S.; Avestro, A.-J.; Ward, T. R.; Sakai, N.; Matile, S. *Angew. Chem., Int. Ed.* **2016**, *55*, 4275–4279. (b) Zhao, Y.; Cotellet, Y.; Avestro, A.-J.; Sakai, N.; Matile, S. *J. Am. Chem. Soc.* **2015**, *137*, 11582–11585.

(17) See SI.

(18) (a) Sakai, N.; Houdebert, D.; Matile, S. *Chem. - Eur. J.* **2003**, *9*, 223–232. (b) Jentzsch, A. V.; Emery, D.; Mareda, J.; Nayak, S. K.; Metrangolo, P.; Resnati, G.; Sakai, N.; Matile, S. *Nat. Commun.* **2012**, *3*, 905.

(19) Bhosale, S.; Matile, S. *Chirality* **2006**, *18*, 849–856.

(20) (a) Adriaenssens, L.; Estarellas, C.; Vargas Jentzsch, A.; Martinez Belmonte, M.; Matile, S.; Ballester, P. *J. Am. Chem. Soc.* **2013**, *135*, 8324–8330. (b) Wang, D.-X.; Wang, M.-X. *J. Am. Chem. Soc.* **2013**, *135*, 892–897. (c) Giese, M.; Albrecht, M.; Ivanova, G.; Valkonen, A.; Rissanen, K. *Supramol. Chem.* **2012**, *24*, 48–55.

(21) (a) Miros, F. N.; Zhao, Y.; Sargsyan, G.; Pupier, M.; Besnard, C.; Beuchat, C.; Mareda, J.; Sakai, N.; Matile, S. *Chem. - Eur. J.* **2016**, *22*, 2648–2657. (b) Miros, F. N.; Matile, S. *ChemistryOpen* **2016**, *5*, 219–226.