The Opening of 1,2-Dithiolanes and 1,2-Diselenolanes: Regioselectivity, Rearrangements, and Consequences for Poly(disulfide)s, Cellular Uptake and Pyruvate Dehydrogenase Complexes

Laurent, Quentin François Antoine; Sakai, Naomi; Matile, Stefan

How to cite

LAURENT, Quentin François Antoine, SAKAI, Naomi, MATILE, Stefan. The Opening of 1,2-Dithiolanes and 1,2-Diselenolanes: Regioselectivity, Rearrangements, and Consequences for Poly(disulfide)s, Cellular Uptake and Pyruvate Dehydrogenase Complexes. In: Helvetica Chimica Acta, 2019, vol. 102, n° 2, p. e1800209. doi: 10.1002/hlca.201800209

This publication URL: https://archive-ouverte.unige.ch/unige:114504
Publication DOI: 10.1002/hlca.201800209

The Opening of 1,2-Dithiolanes and 1,2-Diselenolanes: Regioselectivity, Rearrangements, and Consequences for Poly(disulfide)s, Cellular Uptake and Pyruvate Dehydrogenase Complexes

Quentin Laurent, Naomi Sakai and Stefan Matile*

Department of Organic Chemistry, University of Geneva, Quai Ernest Ansermet 30, CH-1211 Geneva 4, Switzerland, e-mail: stefan.matile@unige.ch

The thiol-mediated opening of 3-alkyl-1,2-dithiolanes and diselenolanes is described. The thiolate nucleophile is shown to react specifically with the secondary chalcogen atom, against steric demand, probably because the primary chalcogen atom provides a better leaving group. Once released, this primary chalcogen atom reacts with the obtained secondary dichalcogenide to produce the constitutional isomer. Thiolate migration to the primary dichalcogenide equilibrates within ~20 ms at rt at a 3:2 ratio in favor of the secondary dichalcogenide. The clarification of this focused question is important for the understanding of multifunctional poly(disulfide)s obtained by ring opening disulfide exchange polymerization of 3-alkyl-1,2-dithiolanes, to rationalize the cellular uptake mediated by 3-alkyl-1,2-diselenolanes as molecular walkers and, perhaps, also of the mode of action of pyruvate dehydrogenase complexes. The isolation of ring-opened diselenolanes is particularly intriguing because dominant selenophilicity disfavors ring opening strongly.

Relaxed acyclic disulfides and diselenides have a CXXC dihedral angle of 90° (X = S, Se, *Figure 1a*).[1-3] This angle is the best to minimize lonepair repulsion and maximize hyperconjugation.[1,2] In 3-alkyl-1,2-dithiolanes, the CXXC dihedral is 35°.[3] The opening of 1,2-dithiolanes **1** by dynamic-covalent thiolate-disulfide exchange with a thiolate **2** releases this ring tension. The ring-opened reactive intermediate can be trapped irreversibly after the addition of thiolate-reactive agents **3**, which converts the thiolates into sulfides. With 3-alkyl-1,2-dithiolanes **1**, thiol-mediated strain release can afford two products, i.e., **4** and **5**, resulting from the reaction of the thiolate **2** with the *secondary* (*sec*) or the *primary* (*pri*) sulfur of the disulfide. The clarification of the regioselectivity between these isomers formed is relevant for the understanding of functional systems in chemistry, biology and the materials sciences.[2,4-22] It determines the tacticity of functional poly(disulfide)s prepared by ring-opening disulfide-exchange polymerization in vesicles,[5] on solid surfaces,[6] and in solution.[7-13] Moreover, similar nucleophilic ring opening of lipoyl amide by acetyl thiamine "*Breslow* intermediates"

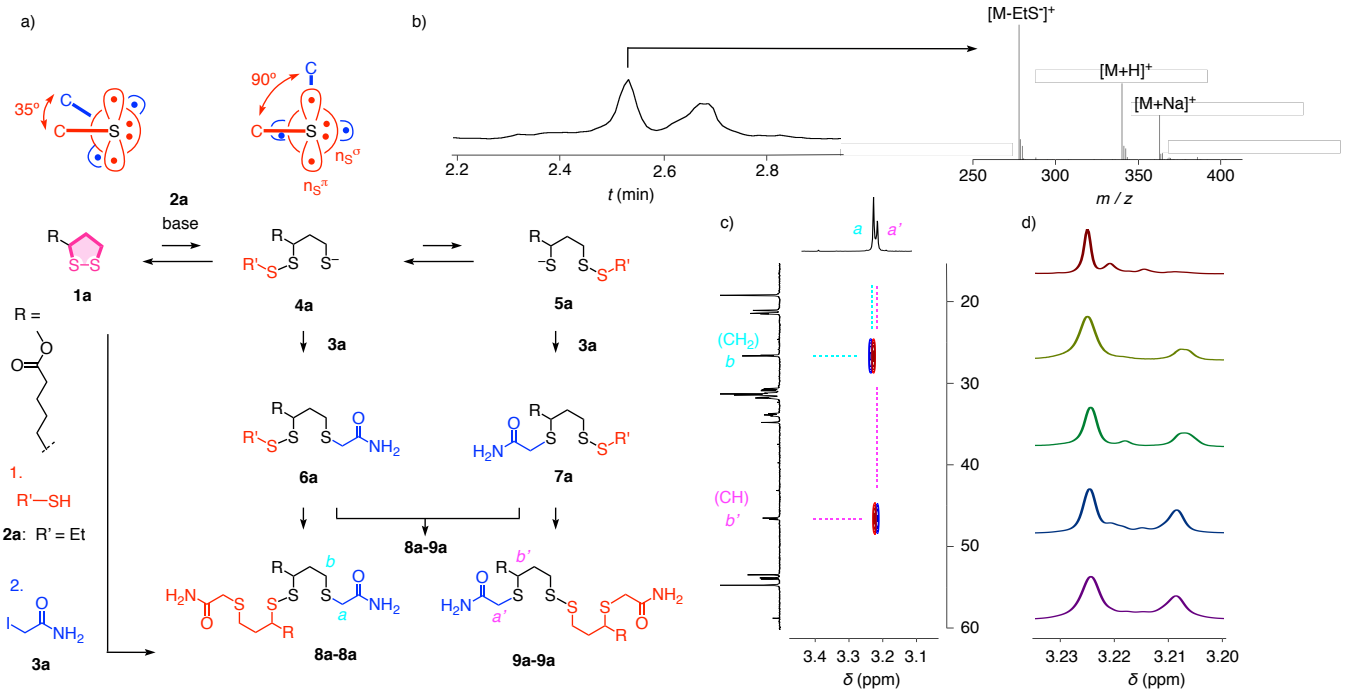

Figure 1. a) Reaction of dithiolane **1a** with thiol under basic conditions (DIPEA) in CH_2Cl_2 at –78 °C followed by quenching with **3a** in CH_2Cl_2 at –78 °C and workup affords dimers of constitutional isomers **8a** and **9a**, with Newman projection of CSSC dihedral angles in **1a** and **4a**. b) LC-MS of product mixture of **1a** reacted with **2a** followed by **3a**, with M of **6a**/**7a**. c) Diagnostic region of the HMBC NMR spectra in $CDCl_3$ to discriminate and quantify isomers **8a** and **9a** in product mixtures. d) ^{1}H NMR spectrum in $CDCl_3$ 10, 20, 30 and 60 s after the addition of **2a** to **1a** at –78 °C (top down) and after 10 s at 0 °C (bottom) in CH_2Cl_2, recorded after quenching with **3a** and workup.

is believed to take place in the enzyme complex that transforms pyruvate into acetyl CoA.[14-22] In his initial model studies, *Ronald Breslow* proposed the nucleophilic attack on the secondary sulfur of lipoic acid.[14] However, later studies supported the kinetic and thermodynamic preference for the attack on the primary rather than the secondary sulfur.[15,16] Many aspects contribute to the regioselectivity in the enzyme active site, particularly hydrogen bonding to histidines and positioning of the partners.

In the following, we answer the question which regioisomer is preferentially formed, show that fast intramolecular rearrangements influence the result, explain why this detailed question is of general interest, and apply the lessons learned to 3-alkyl-1,2-diselenolanes. Recent progress with chalcogen bonding research[23,24] confirmed that this shift of attention from sulfur to selenium is not a simple extension. Because of the longer Se-Se and Se-C bonds, ring tension from lonepair repulsion and losses from hyperconjugation are less pronounced in 1,2-diselenolanes than in 1,2-dithiolanes. As a result, the CXXC dihedral angle decreases from 35° to 0°.[25-28] Moreover, exchange with selenium is much faster than with sulfur (up to seven orders of magnitude),[29] selenols (pK_a ~5) obtained by thiol-

mediated ring opening are more acidic than thiols (pK_a ~ 8), and selenophilicity produces a strong preference for diselenides over mixed selenosulfides.[29-36] As a result, 3-alkyl-1,2-diselenolanes prefer to stay closed, and fast exchange makes it challenging to catch selenosulfides and demonstrate that 1,2-diselenolanes really do exchange with thiolates.[27] In the following, this question is clarified, also with regard to post-exchange rearrangements that may or may not account for the intriguing power of 3-alkyl-1,2-diselenolanes to enter into cells.[27]

To trap the highly reactive monomeric thiolates **4a** and **5a**, the reactions were performed at –78 °C in dichloromethane (*Figure 1a,b*, *Scheme S2*). Ten to sixty seconds after the addition of five equivalents of thiol **2a** and three equivalents of *Hünig* base to dithiolane **1a**, the reactions were quenched at –78 °C with three equivalents of iodoacetamide **3a**. The same processes were repeated four times to improve the conversion. LC-MS of the crude reaction mixtures showed the expected formation of the mixed disulfides **6a** and/or **7a** (*Figure S4*). However, without NMR spectra, the two isomers were indistinguishable, and after the workup, they were replaced by dimeric products **8a-8a**/**8a-9a**/**9a-9a** (*Figure S4*). The apparent conversion of **6a**/**7a** to **8a-8a**/**8a-9a**/**9a-9a** can be rationalized by the continued exchange reactions driven by the evaporation of ethanethiol during workup. As sulfide bonds are irreversible, the product ratio **8a**/**9a** should reflect the ratio of **6a**/**7a**, and thus the selectivity **4a**/**5a**. The ^{1}H NMR spectra of the mixture of dimers displayed two sets of signals originating from the two regioisomers **8a** and **9a** (*Figures 1c, S7-S9*). Two well-resolved singlets at ~3.2 ppm could be assigned by HMBC spectra to acetamide CH_2 protons attached to primary or secondary sulfide. Namely, the cross peak found between the larger downfield peak at ~3.22 ppm and the methylene carbon demonstrate that these peaks originate from the primary sulfide isomer **8a** (*Figure 1c*). The smaller upfield peak at ~3.21 ppm was correspondingly assigned to the protons *a'* in the secondary sulfide isomer **9a**. The integration of the two peaks revealed that the two isomers are obtained at a 3:2 ratio in favor of the primary sulfide **8a**. In the ^{1}H NMR spectra, heterodimer **8a**-**9a** was indistinguishable from homodimers **8a**-**8a** and **9a**-**9a**. The signals coming from the **8a** half are the same whether the other half is **8a** or **9a**. The 3:2 ratio measured is the overall percentage of **8a** and **9a** parts, regardless of their partner in the respective dimers.

The ratio between the two isomers was independent of stereochemistry, results with enantiopure and racemic **1a** were identical (*Figure S11*). The ratio between the two isomers was independent also of thiol **2**: *tert*-Butyl thiol **2b** used in place of ethyl thiol **2a** gave the same result (*Figures S4, S11*). The ratio between the two products did depend on the reaction time allowed for dithiolane **1a** and thiolate **2a** before the addition of **3a**. With short and mild incubation at –78 °C, the primary sulfide **8a** was produced almost exclusively (*Figure 1d*). This result suggested that the thiolate **2a** reacts selectively

with the secondary sulfur atom in disulfide **1a**, thus indicating that superior leaving groups dominate sterics. Increasing yield of the secondary sulfide **9a** with increasing reaction time implied that the secondary disulfide **4a** isomerizes into the primary disulfide **5a**. Under the conditions used, the intramolecular thiolate migration proceeded up to maximal 38% conversion, i.e., an equilibrium constant $K = 0.61$ (*Figure 2b*○). The rate constant $k = 1.74\ 10^{-2}\ s^{-1}$ corresponded to a half lifetime of $t_{50} = 15$ s at –78 °C and an estimated $t_{50} \approx 7$ ms at 25 °C. The slight preference of secondary disulfides **4a** over primary disulfides **5a** in equilibrium was unexpected considering the previous experimental results from the thioesters[15] and oxygen homologs.[37]

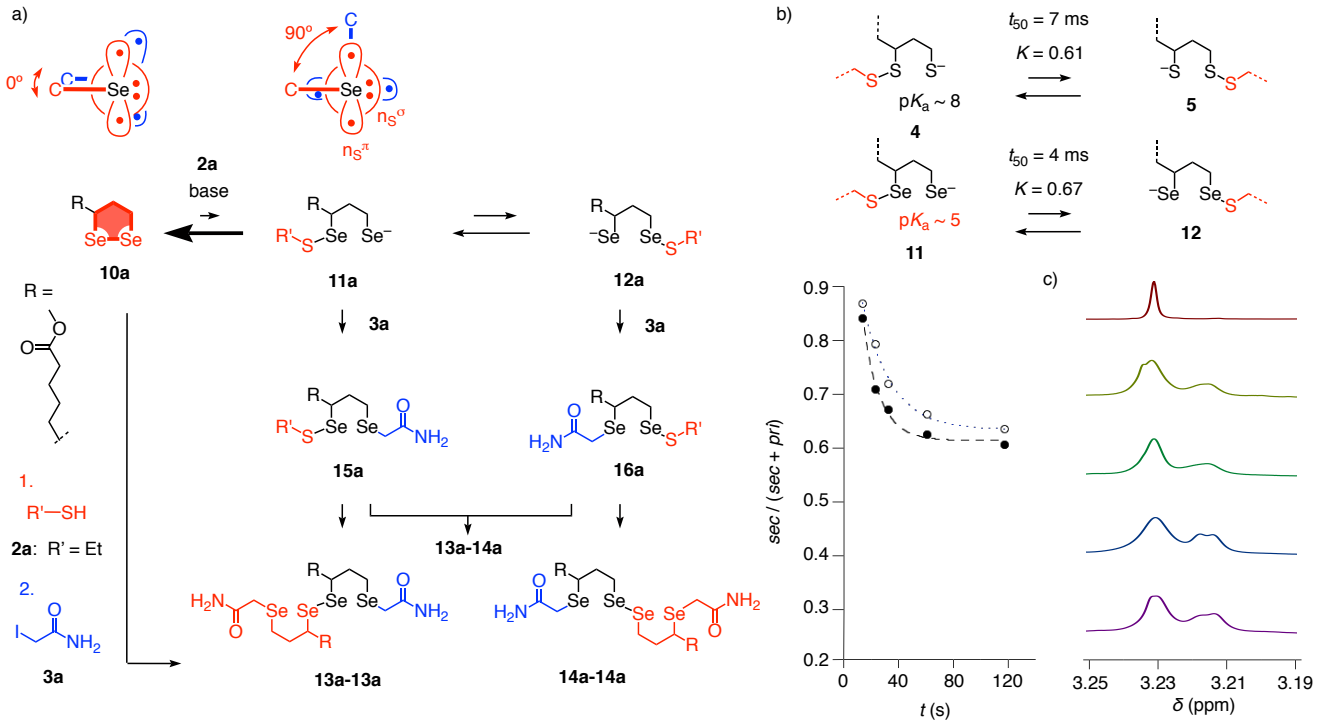

Figure 2. a) Reaction of diselenolane **10a** with thiol **2a** under basic conditions (DIPEA)) in CH_2Cl_2 at –78 °C followed by quenching with **3a** in CH_2Cl_2 at –78 °C and workup affords dimers of constitutional isomers **13a** and **14a**, with Newman projection of CSeSeC dihedral angle in **10a** and **11a**. b) Ratio of *sec* / (*sec* + *pri*) substituted isomers **13a** / (**13a** + **14a**) (●) compared to **8a** / (**8a** + **9a**) (○) as a function of reaction time at –78 °C in CH_2Cl_2 before quenching with **3a**, with graphical general summary of the thiolate-initiated opening of 3-alkyl-1,2-dithiolanes and 3-alkyl-1,2-diselenolanes. c) ^{1}H NMR spectrum in $CDCl_3$ 10, 20, 30 and 60 s after the addition of **2a** to **10a** at –78 °C (top down) and after 10 s at 0 °C (bottom) in CH_2Cl_2, recorded after quenching with **3a** and workup.

The lessons learned with 3-alkyl-1,2-dithiolane **1a** were then used to tackle 3-alkyl-1,2-diselenolane **10a** (*Figure 2*). This move from sulfur to selenium was not as trivial as it might appear. As

mentioned in the introduction, the exchange is faster[29] and, most importantly, the preference of 1,2-diselenolanes to stay closed is very pronounced because the long Se-Se and Se-C bonds reduce ring tension, and selenophilicity overcompensates all remaining tension by far (*Figure 3a*, bold black arrow). Despite earlier difficulties in detecting selenosulfide intermediates,[27] e.g., **11a** and **12a**, the reaction of diselenolane **10a** with thiol **2a** at –78 °C in CH_2Cl_2 followed by trapping of the reactive intermediates with iodoacetamide **3a** afforded products that were consistent with the diselenide dimers **13a-13a**/**13a-14a**/**14a-14a** after workup procedures. The existence of the intermediate selenosulfides **15a** and **16a** was confirmed by LC-MS (*Figure S3*).

As with dithiolane **1a**, diselenolane **10a** opened almost exclusively into the secondary selenosulfide **11a**, which then rearranged into the primary selenosulfide intermediate **12a** with k = 3.03 10^{-2} s^{-1} at -78 °C (*Figure 2b*●). This value corresponded to a t_{50} = 4 ms of **11** at 25 °C. Compared to t_{50} = 7 ms for the opened dithiolane **4** at 25 °C *Figure 2b*○), thiolate migration was thus slightly faster with selenium than with sulfur.

The comparably small difference between S and Se nucleophiles and leaving groups suggested that kinetics are dominated by proximity effects and the nature of the electrophile, that is the migrating thiolate, identical in both systems. This thiolate migration proceeded to 39% yield of the primary selenosulfide **12a** (*Figure 2b*●). The resulting K = 0.67 was close to the K = 0.61 observed with 1,2-dithiolane substrates.

There is consensus in the literature that the involved transformations are all S_N2 reactions. The measured rates were likely to depend on the nature of the thiol nucleophile **2**, the trapping reagent **3**, the base, solvent and temperature. However, the observed trends implied that the introduced strategy to trap reactive intermediates operates as designed. For instance, if trapping with iodoacetamide **3a** would not be faster than the rate of the rearrangements following ring opening, then the observed regioselectivities would not change with time. Significantly selective trapping of one of the two isomers would only matter if the disfavored reaction would also be slower than isomerization. If so, then only the fast reacting isomer would be trapped. If the nature of the base, used in excess, would influence the outcome, then results involving thiols and selenols would have to reflect their difference in acidity (*Figure 2b*). In ethyl acetate instead of dichloromethane, finally, the ratio at equilibrium was unchanged.

Diseleno lipoic acid (DiSeL) derivatives **10** efficiently deliver various substrates to cytosol and nucleus of various cells, including substrates as large as proteins and quantum dots (unpublished).[27] DiSeL-mediated uptake is attractive because it provides a conceptually innovative approach to an important challenge in current biology and beyond. Results with acyclic and 4-substituted controls

and model studies on thiol-exchange affinity columns[27] support that for cellular uptake,[38] DiSeL **10** might function like a molecular walker,[39–42] moving along transmembrane disulfide tracks in membrane proteins (*Figure 3*). The resulting temporary protein denaturation on the one side together with adaptive micellar membrane defects on the other side are compatible with DiSeL-mediated delivery of large substrates. The here reported identification of isomers **11** and **12** provides unprecedented direct experimental evidence in support of this hypothesis, and indicates that the walker takes one step in 4 ms (*Figures 2, 3*).

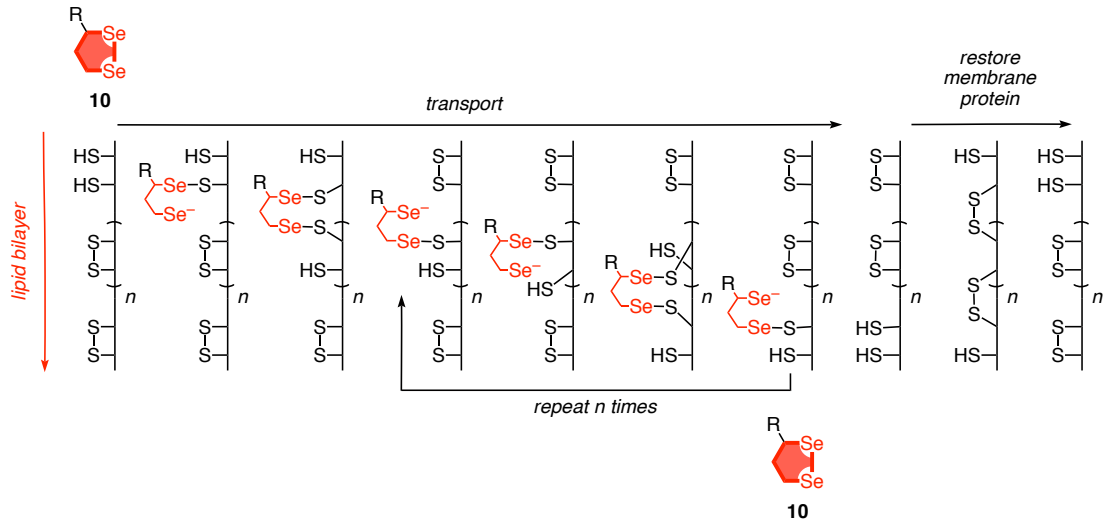

Figure 3. The working hypothesis of the mode of action of DiSeL-mediated cellular uptake, with **10** as molecular walker walking along transmembrane disulfide tracks in membrane proteins.

Our results further demonstrate that dithiolanes could in principle walk almost as fast as diselenolanes into cells. They fail to do so only because contrary to the more acidic selenols, the involved thiols are protonated in neutral water. This protonation inhibits dynamic covalent dichalcogenide exchange after initial, strain-promoted opening by exofacial thiols, the walkers cannot move on after the first step. They remain immobilized on the membrane protein (e.g. the transferrin receptor)[43] and thus accumulate in endosomes with only partial release into the cytosol.[27]

The walker hypothesis for diselenolane-mediated (but not dithiolane-mediated) cellular uptake is related to and endorsed by extensive studies on the catalysis of oxidative protein folding and the repair of misfolded protein with diselenides, shown to occur also *in vivo*.[32–36] Direct experimental support for the walker hypothesis thus implied significance and intriguing perspectives also with regard to the control of oxidative protein folding by dynamic covalent selenium chemistry *in vivo*. Moreover, our

results suggested that diselenolanes **10** should be polymerizable. This perspective of ring-opening diselenide-exchange polymerization is quite attractive.

Concerning the dithiolanes, the here obtained results allow us to assign the structure of poly(disulfide)s, e.g., cell-penetrating poly(disulfide)s (CPDs)[7–13] formed from lipoyl-arginine conjugates **1b** to regioirregular **17** (*Figure 4*). Regioregular *pri*/*sec* (or *head*/*tail*) fused hypothetical polymers HP-**18** would form if polymerization is faster than rearrangement. This might be possible depending on the experimental conditions used (*Figure S5*). However, the more likely structure of CPDs is that of a randomly mixed *pri*/*sec*, *pri*/*pri* and *sec*/*sec* fused polymer **17**, with the ratio of *sec*-first and *pri*-first monomers being at least 3:2. According to the present study, CPDs are not *pri*/*sec*-fused hypothetical polymers HP-**19**. This information on poly(disulfide) structure from the here reported trapping experiments is important because it can hardly be obtained directly from the poorly resolved NMR spectra of the polymers.

In summary, we report experimental evidence that the thiolate-mediated opening of 3-alkyl-1,2-dithiolanes and particularly 1,2-diselenolanes occurs, that the nucleophile attacks specifically on the secondary chalcogen atom and that it is followed by partial fast intramolecular migration to the primary chalcogen atom (*Figure 2b*). We provide pertinent rate and equilibrium constants and explain why the topic is of interest in chemistry, biology and the materials sciences.

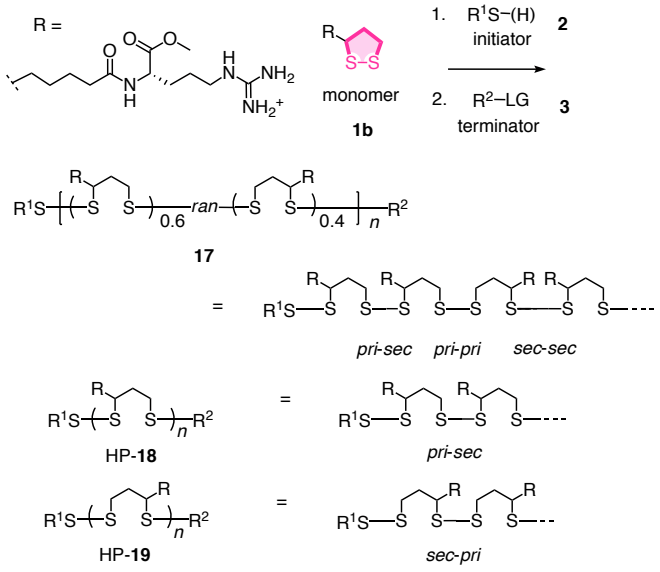

Figure 4. The structure of CPDs is random (*ran*) **17** and neither regioregular HP-**18** nor regioregular HP-**19**.

Supplementary Material

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/MS-number.

Acknowledgements

We thank the NMR and MS platforms for service, and the University of Geneva, the Swiss National Centre of Competence in Research (NCCR) Chemical Biology, the NCCR Molecular Systems Engineering and the Swiss NSF for financial support.

Author Contribution Statement

Q. L., N. S. and S. M. conceived this work, designed the experiments, discussed the results and wrote the manuscript. Q. L. did all the experiments.

References

[1] A. D. Clauss, S. F. Nelsen, M. Ayoub, J. W. Moore, C. R. Landis, F. Weinhold, 'Rabbit-Ears Hybrids, VSEPR Sterics, and Other Orbital Anachronisms', *Chem. Educ. Res. Pract.* **2014**, *15*, 417 – 434.

[2] C. P. Hiberty, B. Braïda, 'Pleading for a Dual Molecular-Orbital/Valence-Bond Culture', *Angew. Chem. Int. Ed.* **2018**, *57*, 5994 – 6002.

[3] R. Singh, G. M. Whitesides, 'Degenerate Intermolecular Thiolate-Disulfide Interchange Involving Cyclic Five-Membered Disulfides Is Faster by ~10^3 Than That Involving Six- or Seven-Membered Disulfides', *J. Am. Chem. Soc.* **1990**, *112*, 6304 – 6309.

[4] E.-K. Bang, M. Lista, G. Sforazzini, N. Sakai, S. Matile, 'Poly(disulfide)s', *Chem. Sci.* **2012**, *3*, 1752 – 1763.

[5] J. Stefely, M. A. Markowitz, S. L. Regen, 'Permeability Characteristics of Lipid Bilayers from Lipoic Acid-Derived Phosphatidylcholines. Comparison of Monomeric, Crosslinked and Noncrosslinked Polymerized Membranes', *J. Am. Chem. Soc.* **1988**, *110*, 7463 – 7469.

[6] H. Hayashi, A. Sobczuk, A. Bolag, N. Sakai, S. Matile, 'Antiparallel Three-Component Gradients in Double-Channel Surface Architectures', *Chem. Sci.* **2014**, *5*, 4610 – 4614.

[7] E.-K. Bang, G. Gasparini, G. Molinard, A. Roux, N. Sakai, S. Matile, 'Substrate-Initiated Synthesis of Cell-Penetrating Poly(disulfide)s', *J. Am. Chem. Soc.* **2013**, *135*, 2088 – 2091.

[8] P. Morelli, E. Bartolami, N. Sakai, S. Matile, 'Glycosylated Cell-Penetrating Poly(disulfide)s: Multifunctional Cellular Uptake at High Solubility', *Helv. Chim. Acta* **2018**, *101*, e1700266.

[9] P. Morelli, S. Matile, 'Sidechain Engineering in Cell-Penetrating Poly(disulfide)s', *Helv. Chim. Acta* **2017**, *100*, e1600370.

[10] J. Fu, C. Yu, L. Li, S. Q. Yao, 'Intracellular Delivery of Functional Proteins and Native Drugs by Cell-Penetrating Poly(disulfide)s', *J. Am. Chem. Soc.* **2015**, *137*, 12153 – 12160.

[11] L. Qian, J. Fu, P. Yuan, S. Du, W. Huang, L. Li, S. Q. Yao, 'Intracellular Delivery of Native Proteins Facilitated by Cell-Penetrating Poly(disulfide)s', *Angew. Chem. Int. Ed.* **2018**, *57*, 1532 – 1536.

[12] G. A. Barcan, X. Whang, R. M. Waymouth, 'Structurally Dynamic Hydrogels Derived from 1,2-Dithiolanes', *J. Am. Chem. Soc.* **2015**, *137*, 5650 – 5653.

[13] X. Zhang, R. M. Waymouth, '1,2-Dithiolane-Derived Dynamic, Covalent Materials: Cooperative Self-Assembly and Reversible Cross-Linking' *J. Am. Chem. Soc.* **2017**, *139*, 3822 – 3833.

[14] R. Breslow, 'The Mechanism of Thiamine Action: Predictions from Model Experiments', *Ann. N. Y. Acad. Sci.* **1962**, *98*, 445 – 452.

[15] E. H. Smith, 'Regioselective Cleavage of the Dithiolane S-S Bond of (+)-a-Lipoic Acid by Carbon and Phosphorus Nucleophiles', *J. Chem. Soc., Perkin Trans.* **1984**, *0*, 523 – 527.

[16] Y.-S. Yang, P. A. Frey, 'Dihydroplipoyl Transacetylase of *Escherichia Coli*. Formation of 8-*S*-Acetyldihydrolipoamide', *Biochemistry* **1986**, *25*, 8173 – 8178.

[17] F. Jordan, 'Current mechanistic understanding of thiamin diphosphate-dependent enzymatic reactions', *Nat. Prod. Rep.*, **2003**, *20*, 184 – 201.

[18] X. Y. Pei, C. M. Titman, R. A. W. Frank, F. J. Leeper, B. F. Luisi, 'Snapshots of Catalysis in the E1 Subunit of the Pyruvate Dehydrogenase Multienzyme Complex', *Structure* **2008**, *16*, 1860 – 1872.

[19] K. Tittmann, 'Reaction Mechanisms of Thiamin Diphosphate Enzymes: Redox Reactions', *FEBS J.* **2009**, *276*, 2454 – 2468.

[20] X. Sheng, Y. Liu, 'Theoretical Study of the Catalytic Mechanism of E1 Subunit of Pyruvate Dehydrogenase Multienzyme Complex from *Bacillus stearothermophilus*', *Biochemistry* **2013**, *52*, 8079 – 8093.

[21] I. Wheeldon, S. D. Minteer, S. Banta, S. Calabrese Barton, P. Atanassov, M. Sigman, 'Substrate Channelling as an Approach to Cascade Reactions', *Nat. Chem.* **2016**, *8*, 299 – 309.

[22] R. N. Perham, 'Swinging Arms and Swinging Domains in Multifunctional Enzymes: Catalytic Machines for Multistep Reactions', *Annu. Rev. Biochem.* **2000**, *69*, 961 – 1004.

[23] S. Benz, C. Besnard, S. Matile, 'Catalysis with Chalcogen Bonds: From Neutral to Cationic Benzodiselenazole Scaffolds', *Helv. Chim. Acta* **2018**, *101*, e1800075.

[24] M. Macchione, M. Tsemperouli, A. Goujon, A. R. Mallia, A. Sakai, K. Sugihara, S. Matile, 'Mechanosensitive Oligodithienothiophenes: Transmembrane Anion Transport Along Chalcogen-Bonding Cascades', *Helv. Chim. Acta* **2018**, *101*, e1800014.

[25] J. Hildebrandt, T. Niksch, R. Trautwein, N. Häfner, H. Görls, M.-C. Barth, M. Dürst, I. B. Runnebaum, W. Weigand, 'Asparagusic Acid Derivatives and Their Cytotoxic Platinum(II) Complexes', *Phosphorus Sulfur Silicon Relat. Elem.* **2017**, *192*, 182 – 186.

[26] T. Niksch, H. Görls, M. Friedrich, R. Oilunkaniemi, R. Laitinen, W. Weigand, 'Synthesis and Characterisation of 2,2-Bis(hydroxymethyl)-1,3-Diselenolato Metal(II) Complexes Bearing Various Phosphanes', *Eur. J. Inorg. Chem.* **2010**, 74 – 94.

[27] N. Chuard, A. I. Poblador-Bahamonde, L. Zong, E. Bartolami, J. Hiltebrandt, W. Weigand, N. Sakai, S. Matile, 'Diselenolane-Mediated Cellular Uptake', *Chem. Sci.* **2018**, *9*, 1860 – 1866.

[28] L. Zong, E. Bartolami, D. Abegg, A. Adibekian, N. Sakai, S. Matile, 'Epidithiodiketopiperazines: Strain-Promoted Thiol-Mediated Cellular Uptake at the Highest Tension', *ACS Cent. Sci.* **2017**, *3*, 449 – 453.

[29] D. Steinmann, T. Nauser, W. H. Koppenol, 'Selenium and Sulfur in Exchange Reactions: A Comparative Study', *J. Org. Chem.* **2010**, *75*, 6696 – 6699.

[30] B. Rasmussen, A. Sorensen, H. Gotfredsen. M. Pittelkow, 'Dynamic Combinatorial Chemistry with Diselenides and Disulfides in Water', *Chem. Commun.* **2014**, *50*, 3716 – 3718.

[31] J. Sayers, R. J. Payne, N. Winssinger, 'Peptide Nucleic Acid-Templated Selenocysteine-Selenoester Ligation Enables Rapid miRNA Detection', *Chem. Sci.* **2018**, *9*, 896 – 903.

[32] J. Beld, K. J. Woycechowsky, D. Hilvert, 'Catalysis of Oxidative Protein Folding by Small-Molecule Diselenides', *Biochemistry* **2008**, *47*, 6985–6987.

[33] N. Metanis, D. Hilvert, 'Harnessing Selenocysteine Reactivity for Oxidative Protein Folding', *Chem. Sci.* **2015**, *6*, 322–325.

[34] J. Beld, K. Woycechowsky, D. Hilvert, 'Small-Molecule Diselenides Catalyze Oxidative Protein Folding *in Vivo*', *ACS Chem. Biol.* **2010**, *5*, 177–182.

[35] S. Shimodaira, Y. Asano, K. Arai, M. Iwaoka, 'Selenoglutathione Diselenide: Unique Redox Reactions in the GPx-Like Catalytic Cycle and Repairing of Disulfide Bonds in Scrambled Protein', *Biochemistry* **2017**, *56*, 5644−5653.

[36] J. C. Lukesh, B. VanVeller, R. T. Raines, 'Thiols and Selenols as Electron-Relay Catalysts for Disulfide-Bond Reduction', *Angew. Chem. Int. Ed.* **2013**, *52*, 12901 – 12904.

[37] J. Chevallier, N. Sakai, F. Robert, T. Kobayashi, J. Gruenberg, S. Matile, 'Rapid Access to Synthetic Lysobisphosphatidic Acids Using P^{III} Chemistry', *Org. Lett.* **2000**, *2*, 1859 – 1861.

[38] M. Grogg, D. Hilvert, M. Ebert, A. Beck, D. Seebach, F. Kurth, P. Dittrich, C. Sparr, S. Wittlin, M. Rottmann, P. Mäser, 'Cell Penetration, Herbicidal Activity, and in-vivo-Toxicity of Oligo-Arginine

Derivatives and of Novel Guanidinium-Rich Compounds Derived from the Biopolymer Cyanophycin', *Helv. Chim. Acta* **2018**, *101*, e18000112.

[39] A. G. Campaña, D. A. Leigh, U. Lewandowska, 'One-Dimsnsional Random Walk of a Synthetic Small Molecule Toward a Thermodynamic Sink', *J. Am. Chem. Soc.* **2013**, *135*, 8639 – 8645.

[40] M. J. Barrell, A. G. Campaña, M. von Delius, E: M. Geertsema, D. A. Leigh, 'Light-Driven Transport of a Molecular Walker in Either Direction along a Molecular Track', *Angew. Chem. Int. Ed.* **2011**, *50*, 285 – 290.

[41] J.-S. Shin, N. A. Pierce, 'A Synthetic DNA Walker for Molecular Transport', *J. Am. Chem. Soc.* **2004**, *126*, 10834 – 10835.

[42] H. D. Winkler, D. P. Weimann, A. Springer, C. A. Schalley, 'Dynamic Motion in Crown Ether Dendrimer Complexes: A "Spacewalk" on the Molecular Scale', *Angew. Chem. Int. Ed.* **2009**, *48*, 7246–7250.

[43] A. Abegg, G. Gasparini, D. G. Hoch, A. Shuster, E. Bartolami, S. Matile, A. Adibekian, 'Strained Cyclic Disulfides Enable Cellular Uptake by Reacting with the Transferrin Receptor', *J. Am. Chem. Soc.* **2017**, *139*, 231–238.