

Squeezing out the catalysts: the disulphide bond exchange in aryl disulphides at high hydrostatic pressure

Szymon Sobczak,* Paulina Ratajczyk and Andrzej Katrusiak*

Faculty of Chemistry, Adam Mickiewicz University, Uniwersytetu Poznańskiego 8, 61-614 Poznań, Poland

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ABSTRACT: Exchange of the disulphide bond is a prominent example of equilibrium reactions. Therefore, the wide library of disulphide exchange reactions requires the application of catalysts, such as reducing agents, strong bases, ultraviolet light, or ultrasounds to stimulate higher conversion yields. The recent observation of pressure-induced exchange of aryl disulphides in the absence of catalysts or other stimuli prompted our study on the mechanism explaining the effect of high pressure on the reaction equilibrium. We employed the pressure between 100 and 400 MPa, for promoting the exchange reactions between various homodimeric aryl disulphides and for optimized conditions obtained 100 % yields in pure single-crystal form of the heterodimer. The reactions were performed in a diamond-anvil cell, as well as in a hydraulic piston-and-cylinder press, and the products were characterized by X-ray diffraction, mass and NMR spectroscopy. The prominent role of high-entropy states, not attainable at ambient conditions, as well as the high-entropy nucleation, kinetic crystallization and other effects associated with the high-pressure environment, is apparent. This entropy-driven reactions are an efficient, environmentally-friendly, one-pot method for obtaining pure crystalline heterodimeric disulphides.

INTRODUCTION

Aryl disulphides find versatile applications owing to the properties of the C–S bond. This is in the coatings of metal surfaces, anticorrosive agents, paints, oils, and lubricants^{1–3} as well as in active pharmaceuticals ingredients (e.g. in Lansoprazole, Sulindac, Esomeprazole, and Quetiapine) used to treat cancer, inflammation, asthma, Alzheimer, Parkinson, HIV and other diseases.^{4–10} Reversible exchange of disulphide bonds underlies living functions, contributing to the stability of the native conformations of proteins.^{11,12} The sensitivity of disulphide metathesis to environmental stimuli has been employed in dynamic covalent chemistry (DCC).^{13–16} Contrary to traditional organic synthesis performed under kinetic regime, DCC involves thermodynamic control of reactions, which results in the spontaneous elimination of less stable products. Conversely, in kinetically controlled reactions, the form of substrates and catalysts, as well as reaction conditions, must be carefully chosen in order to favour the target products over other substrates and possible intermediates.¹³ In most reversible disulphide systems, exchange reactions proceed by nucleophilic attack of a free thiolate at the disulphide bond and often require long equilibration times, even in the presence of a catalysts, which limits their applications.¹⁶ Only recently some significant progress towards cleaner and more efficient methods of disulphide metathesis was reported.^{17–22} A Brønsted base-free method requiring a phosphine to facilitate the reaction was described by Ramstrom *et al.*¹⁸ Belenguer, Friscic and Sanders used mechanochemistry for high-conversion disulphide metathesis in the presence of 1,8-diazabicyclo[5.4.0]undec-7-

ene.^{17,20} Pittelkow's group found that diselenides spontaneously exchange in water and can be used to catalyse disulphide exchange.²¹ Fritze and Delius showed that ultrasounds support the exchange of disulphides in CH₃Cl.¹⁹ Most recently, we have shown that high pressure can promote the metathesis between homodimeric bis(4-chlorophenyl)disulphide with bis(2-nitrophenyl)disulphide without any catalyst or reducing agents and the heterodimeric product was obtained in several solvents.²³

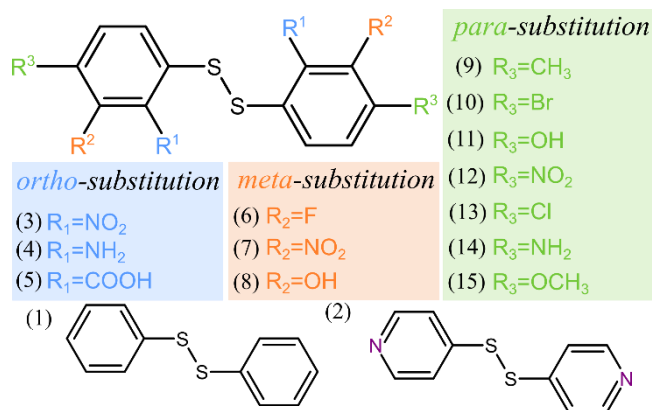


Figure 1. Aryl disulphides investigated under high-pressure. The colour code indicates molecules which are: (blue) *ortho*-; (red) *meta*-; and (green) *para*-substituted.

Presently, we have explored the mechanism of pressure-induced disulphides metathesis. For this purpose, we have performed in a diamond-anvil cell (DAC) 35 reactions between 15 homodimeric disulphides that differ in the

character, size and position of their substituents. The effects of strongly electron withdrawing groups (EWG) COOH and NO₂, electron donating groups (EDG) NH₂, OCH₃, CH₃, OH, as well as halides displaying dual positive-mesomeric and negative-induction features (Cl, Br and F) have been studied and compared. Reactions were conducted in three different solvents: polar protic isopropanol, methanol, as well as polar aprotic acetonitrile. They remain liquid in the range of our high-pressure experiments and secure the hydrostatic conditions.^{24,25} Due to low freezing pressure the nonpolar solvents were not considered for this experiments. Under pressure and without catalyst, we have obtained 21 different heterodimeric aryl disulphides. In six cases, after optimizing reaction the conditions, the products precipitate as single crystals and their structures could be determined by X-ray diffraction. The formation of 15 other products has been confirmed by mass spectrometry. Our results reveal the role of high-pressure reactions and their advantages for the DCC.

RESULTS AND DISCUSSION

It was established that high pressure increases the rate of reaction allowing it to run at lower temperatures. Among the most prominent reactions accelerated by high-pressure are Diels-Alder reactions, 1,3-dipolar cycloadditions, [2+2] cycloadditions, sigmatropic rearrangements and radical polymerizations. Although the impact of pressure on the reaction equilibrium is intuitive, it must be considered on several levels. At the molecular scale, when new bonds are formed, the reaction is accelerated by pressure due to reduced of intermolecular distances and molecular volume. The reverse reaction, a homolytic bond cleavage, increased the volume and shifts the equilibrium toward the reactants.²⁶ The compression, however, does not affect only the molecules themselves, but all reaction system changes its properties.

Under pressure the void spaces and distances between molecules are reduced, so is the space necessary for thermally induced motion and collisions. Additionally, the physical properties of the liquid environment are altered, resulting in higher boiling point, increased density, viscosity and the solubility of most compounds is reduced.

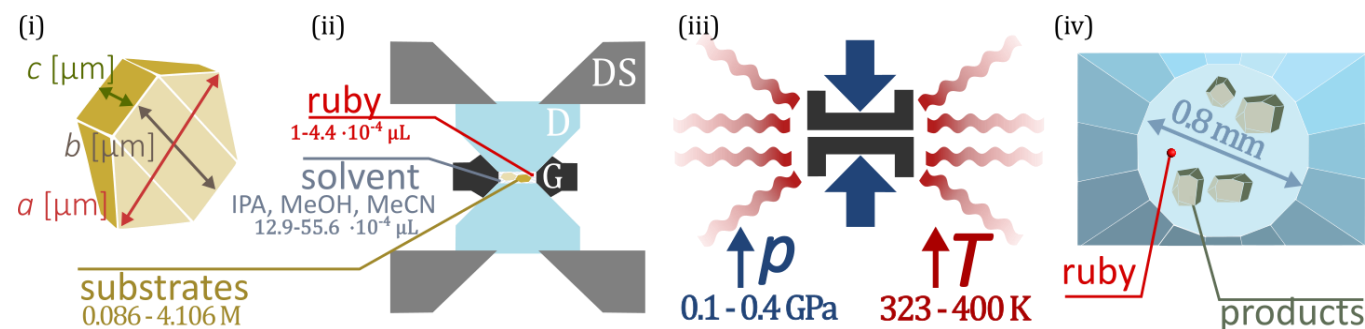


Figure 2. Schematic illustration of high-pressure reaction procedure: (i) single crystal measurements; (ii) loading the DAC chamber with two homodimeric substrates, together with ruby spheres, and filling the remaining volume with the solvent, 2-propanol (IPA), methanol (MeOH) or acetonitrile (MeCN), the DAC consists of two parallel diamonds (D) supported by steel discs (DS) and squeezed metal gasket (G); (iii) compression and heating of the DAC reactor till the dissolution of substrates; and (iv) recovering and analysis of the solid precipitate

Reaction procedure and optimization

We performed a series of high-pressure reactions in a DAC, used as the high-pressure reactor. The DAC was modified by mounting the diamonds directly on the steel supports.²⁷ All reactions were conducted according to the same procedure (Figure 2). Two homodimeric substrates in the form of single crystal were inspected through a microscope and their grains of equal $V_{si} d_i / m_{si}$ (V_{si} , d_i and M_{si} are the grain volume, density and molecular weight of substrate, respectively) were selected in order to obtain 1:1 molar ratio. Then the grains were loaded into the DAC chamber, together with small ruby spheres for pressure calibration.^{28,29} Then the DAC chamber was filled with a solvent, sealed and compressed. The solvent volume (V_{sol}) is:

$$V_{sol} = V_{DAC} - [(V_{si} + V_{sii}) + V_r],$$

where V_{DAC} is the DAC chamber volume, and V_r is the volume of the ruby sphere, and the molar concentration (c_i) of substrates is

$$c_i = (V_{si} \times d_{si} / M_{si}) / V_{sol}.$$

Then the DAC was heated until both reactants dissolved. Depending on the experiment - the substrates, their concentration, the solvent and pressure - the dissolution required the temperature from 323 K to 400 K. After dissolving the substrates, the DAC was cooled down, and when the DAC chamber was unsealed the solvent evaporated. The crude solid precipitate was analyzed by a direct insertion probe-mass spectrometry (DIP-MS) and X-ray diffraction.

The DIP-MS does not require gas chromatographic separation, which eliminates the possibility of the reverse reaction in the analyzed product. High-temperatures used to sample ionization in DIP-MS technique, could be responsible for fragmentation of product/substrate molecules in the analysed sample; therefore, the DIP-MS was used mainly for quickly evaluating the yield. The reaction conditions were optimized by repeating it several times for different concentrations, solvents, pressures and temperatures. For 6 out of 21 reactions (Sections 3 in SI), the yields approached 100% and precipitate in a form of single crystals of quality sufficiently high for X-ray structural study.

The crystals of heterodimeric products were recovered from the DAC chamber and analyzed on a SuperNova diffractometer equipped with a microfocus X-ray tube (detailed crystallographic data are summarized in Table S39, in Section 7 of Supporting Information). In order to establish the reaction equilibria in the solution for successfully exchanged systems (11/14; 3/14; 9/13; 4/13; 4/12; 4/9; 4/7; 1/2; 10/12; 3/9; 3/10), at ambient- and high-pressure, we have collected ^{13}C -NMR spectra of homodimeric mixtures in 2-propanol- d_8 and CD_3CN before and after compression to 0.4 GPa (for the experiment procedure look at 1.2.1 and for obtained spectra Section 5 of SI). The solubility of **3**, **12** and **5** in 2-propanol- d_8 and CD_3CN at ambient conditions was extremely small (spectra 5.1.4 and 5.1.10 of Section 5 in SI). The ^{13}C -NMR spectrum of **5**, could be collected only in $\text{DMSO}-d_6$ (5.1.12 of SI). The observed in liquid yield, for reactions 11/14; 3/14; 9/13; 4/13 and 3/9, was additionally confirmed by DIP-MS (Section 5.5 of SI).

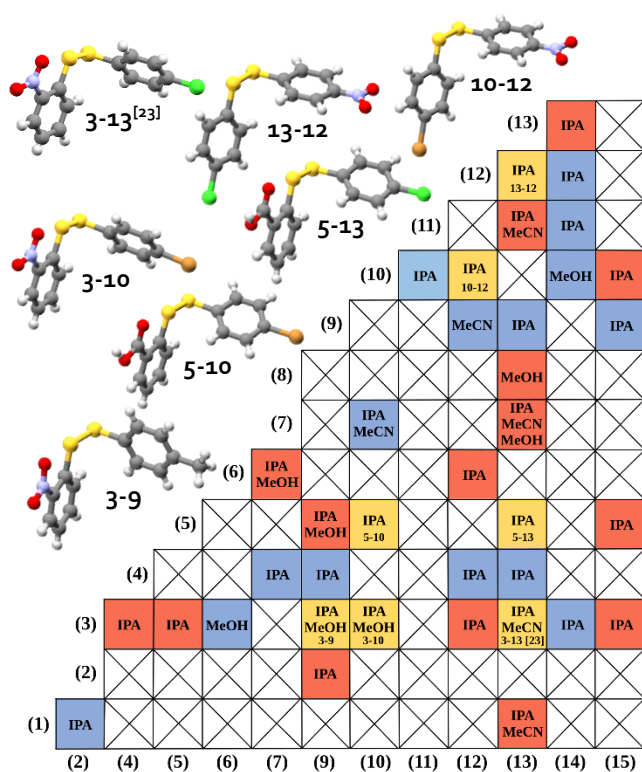


Figure 3. Compilation of all high-pressure reactions presently investigated; the numbers in brackets label the substrates in Figure 1. Yellow colour mark the high-yield heterodimer products characterized by X-ray diffraction; blue – are products detected by DIP-MS spectra and red - no heterodimer traces. Crosses indicate that no reactions were performed. The solvents are indicated: MeOH-methanol, IPA-isopropanol, MeCN-acetonitrile. The inset show heterodimers obtained in a form of single crystals.

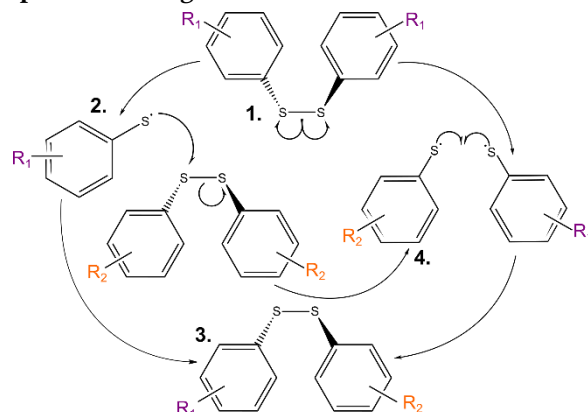
The effect of temperature on solid homodimeric mixture during slow heating to 673 K was investigated by TG-DSC. No thermal effects associated with chemical reac-

tion were detected (Sections 6.1 in SI). The influence of anisotropic pressure on the mixtures of solid homodimers with and without a few drops (4–5 μL) of IPA, was investigated by powder X-ray diffraction, showed no traces of heterodimeric products (Sections 6.2 in SI).

High-pressure chemistry

The control over the high-pressure reactions, as at ambient conditions, can be achieved by two different basic approaches. In a kinetically controlled reaction, the differences between the volume of activation V^\ddagger , which according to transition state theory, is a difference between the partial molar volumes of the transition state and the sums of the partial volumes of the reactants at the same temperature and pressure; leading to the different molecules must be achieved. Alteration of V^\ddagger , can be achieved either by a pressure-induced change of reaction mechanism or can be gained in difference between the volumes of the transition structures within the same, or at least similar, mechanism. In a thermodynamically controlled reaction, its rate increases when reaction volume, V^0 , decreases. Recently, it was shown both theoretically and experimentally that instead of proposed before [2 + 2] metathesis, the S-S reversible bond cleavage and formation, is radical-mediated (Scheme 1).^{30–34} According to this mechanism, the reaction initiates when sulfenyl radicals are formed (step 1). Bond dissociation is a process associated with a volume expansion and, at high-pressures, it is reaction rate determining step. This process does not resemble the UV or ultrasounds generation of radicals but rather chain reaction where a positive feedback leads to a self-amplifying chain of events.

Scheme 1. Mechanisms of an [2+1] radical mediated disulphide exchange



The formation of sulfenyl radicals strongly depends on S-S bond energy. Theoretical studies on disulphide based polymers connect the S-S length with bond energy in an inverse correlation.³³ Our survey of the molecular structures of homodimeric aryl disulphides reported in this work and those deposited in the Cambridge Structural Database (CSD Version 5.41, ConQuest Version 2.05, Figure S1) show that the substitution of EDG in *para*- or *ortho*- or EWG in *ortho*-

position, as well as the presence of a heteroatom in the aromatic ring, result in longer S-S distances. It appears that a substitution by the EDG adds electron density to a conjugated π -system *via* resonance or inductive effects. This increase in electron density into the antibonding σ_{ss}^* bond, followed by elongation of the S-S bond, lowers its dissociation energy. Similarly, the *ortho*-positioned EWG, due to the resonance effect, creates an electron-deficient (δ^+) region at the S-atom and weakens the S-S bond. In contrast, *para*-substituted EWG have an opposite effect, shortening the S-S bond. At high-pressures, the energy necessary for bond dissociation can be achieved at lower temperatures, what is more indeed the recrystallization of **9**,³⁵ was connected with S-S bond elongation from 2.024 Å at ambient conditions to 2.058 Å at 0.45 GPa. Once free radicals are generated, they attack other homodimers and produce a new free radical (step 2), along with a product molecule (step 3). At this stage, the reverse recombinations are also possible. Although at high-pressure the reverse reaction can only occur if formation of product would lead to negligible reduction of V^0 . The reaction terminates when two different radical species react with each other to form a heterodimeric adduct (step 4). In order to resolve if the pressure reactions in DAC chamber (conducted in the solid-solute-solid sequence, cf. section: *Reaction procedure and optimization*) are proceed under thermodynamic or kinetic i.e. the reactions are generally characterized by negative V^0 or there is some kinetic aspect involved, we compared the results with the pressure effect on compressed mixtures of homodimers dissolved in 2-propanol-d8 and CD₃CN. For equilibrium reactions with large negative V^0 , the application of high pressure would lead to a significant yield increase. This relationship comes from the fact that a small change in free Gibbs energy (ΔG^0) leads to a logarithmically amplified change in equilibrium position, according to;

$$\Delta G^0 = \partial \ln K / \partial p T = -\Delta V^0 / RT,$$

where R is the ideal gas constant, T temperature and K the equilibrium constant.

A kinetic study has been performed for 11 different systems, corresponding to reactions successfully conducted in the DAC. Homodimers were first dissolved in 2-propanol-d8 and CD₃CN, then mixed and after 12h in ambient conditions, their ¹³C-NMR spectra were collected. In seven systems (11/14; 9/13; 3/14; 10/12; 3/9; 3/10; 4/12) no product was observed, while in four other reactions an equilibrium established below 50% of the product. Next, these same systems were compressed isothermally at 0.4 GPa and their spectra were collected within a 0.5 h after pressure was released. Surprisingly, compression of the dissolved homodimers, in reactions between 11/14; 3/14; 10/12; 3/9; 3/10; 4/12 still did not result in formation of the heterodimer product (cf. SI). We have connected these different results with the intrinsic volume profiles of the reactions (Figure 4), based on van der Waals models of substrate and product molecules. Owe to significantly different volume of substituents R_i in substrates (Figure 1), the molecular volume of the heterodimer is close to the intermediate of the volumes of

homodimers. Subtle departures from the mean value (ΔV_m) are mainly due to the S-S bond length changes (ΔL), according to approximate formula $\Delta V_m \approx 18.3 \Delta L$ [Å³]. The S-S length change of 0.07 Å, e.g. between 2.01 and 2.07 Å, corresponds to $\Delta V_m = 1.0$ Å³ comparable to the accuracy of our volume calculations.

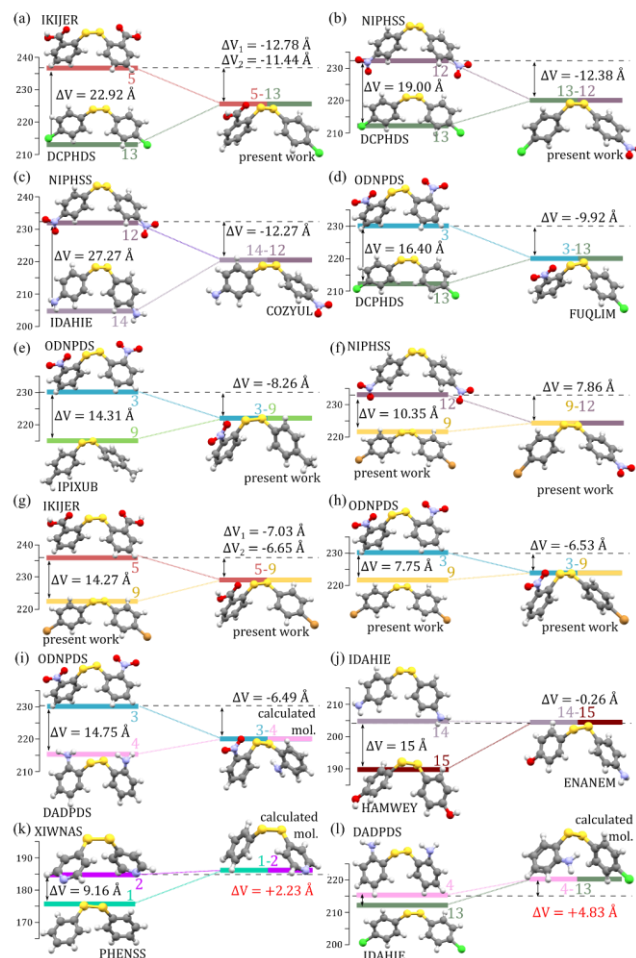


Figure 4. Van der Waals volumes profile calculated for the exchange reaction. The structures were determined in this work, or retrieved from the CSD (where six-letter refcodes are given). For reactions 3/4, 1/2, 4/13 the molecular conformation of product molecule has been calculated in program Gaussian16 with B3LYP/6-311+ G (2d, 2p) level of theory.

The molecular conformation is another variable capable of stimulating the heterodimers formation at high-pressure.³⁶ The intermolecular interactions can considerably change soft conformational parameters and may be relevant for improving the reactivity of disulphides.^{22,37} It was suggested for free radical polymerization of ethylene that the formation of various supramolecular intermediate forms can be unique for high-pressure conditions and thus essential for the increase in conversion to the product form.³⁸ In all heterodimeric disulphides the C-S-S-C torsional angles are all within $\pm(85^\circ \pm 3^\circ)$. The value of this torsion angle is dominated by 3p lone pairs on the two S atoms, which minimize

their mutual overlap and repulsion integrals for the orthogonal position.³⁹

Control by the Entropy

The synthesis of heterodimers (AB) from homodimers (A_2 and B_2) can be achieved, even with 100% yield, in the entropy-driven kinetic process schematically depicted in Figure 5. The process consists of several stages, which initially maximizes the entropy (S) of the system and then triggers the crystallization of the heterodimer. High pressure plays an essential role, allowing the entropy to increase beyond that attainable at atmospheric pressure. Thus, at stage 1 this system consisting of equimolar amounts of homodimers A_2 and B_2 and some solvent (F) is closed in a DAC chamber. The chamber is sealed and pressurized to about 200 MPa (2000 bar). This adds the compression work component to the Gibbs free energy (G) and most of homodimers A_2 and B_2 remain in crystalline form. The solubility usually decreases with increasing pressure, so apart from the work contribution (pV) the entropy (S) decreases due to a smaller portion of the crystals dissolved at stage 2 compared to stage 1. In stage 3, the sample is heated up until stage 4, when crystals A_2 and B_2 dissolve. At this point, the system assumes the maximum entropy when molecules A_2 , B_2 and F are randomly mixed. At this stage the dimers still increase entropy through their environmental variation. Accordingly, to the experimental reports, and also to the theoretical calculations, at high pressure the S-S distance significantly increase facilitating the bond cleavage; also the disulphide conformation can change and become more ‘open’ to be attacked by sulfenyl radical.^{22,37,40} Then the entropy can be further increased at still higher temperature when the homodimers start to dissociate into radicals at stage 5. The increased number of radicals intensifies the chain reactions, leading to heterodimers AB, whereas some recombinations to A_2 and B_2 when the product and substrate are both comparable in volume. On lowering the temperature, the system (stage 6) tends to reduce the entropy while the ratio between the homo- and heterodimers depends on the equilibrium in the solution at given thermodynamic conditions. At stage 7, a significant reduction of entropy is achieved by the process of nucleation.

It is characteristic of high temperature that particles are well mixed, as the grouping of identical particles would decrease the entropy. This strongly favours the nucleation of heterodimers. At stage 7, the solubility of A_2 , B_2 and AB in solvent is very important as the low solubility of heterodimer AB increases its chances to nucleate. The kinetic crystallization of AB shifts the reaction equilibrium toward the product side and fuels the synthesis of heterodimers AB. At the final stage 8, at 296 K, all homodimers reacted into heterodimers are present in the solid form of one or more solid grains except for the small numbers of A_2 , B_2 and AB dimers (hence low entropy S) remaining dissolved in solution. Kinetic crystallization following the reduction of temperature strongly reduces the entropy because just one substance is ordered in the crystal. It is apparent that the solubility of AB compared

to those of A_2 and B_2 is important for nucleation. It is reasonable to assume that relative to homodimers, the polarity of heterodimeric molecules significantly increases, which in turn increases the electrostatic cohesion forces and reduces the crystals solubility.

It should be stressed, that high-pressure is used as an efficient method of sealing the system. For a closed system, the entropy can be increased to the required level (stage 5) of strongly mixed molecules and radicals. After stage 7, the confining role of the DAC chamber is continued, irrespective of the pressure value, which can be kept high or released.

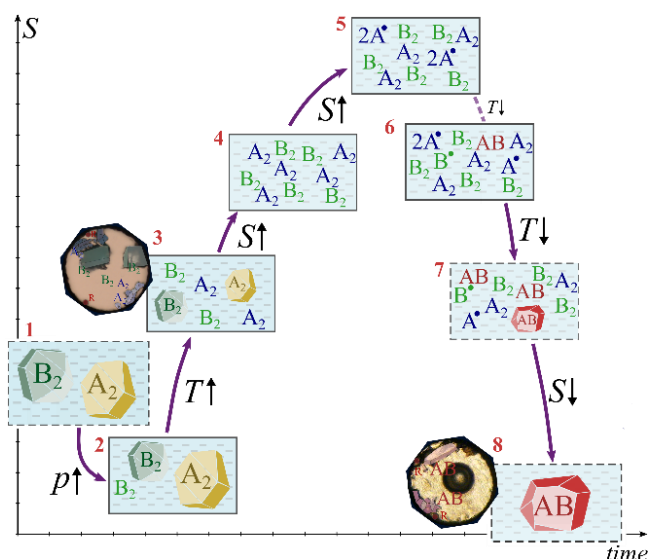


Figure 5. Schematic illustration of the entropy driven synthesis of heterodimers AB from homodimers A_2 and B_2 dissolved in solvent (grey dashes). The stages of the process (red numbers) are described in the text. The open and closed systems has been indicated by the dashed and solid edges of boxes, respectively.

CONCLUSIONS

Disulphide exchange reactions have been systematically investigated for a series of representative, and in some cases unique, aryl disulphides with distinct chemical features, in different environments and in extreme conditions of high-pressure and high-temperature. These results provide a microscopic insight into non-catalytic disulphide exchange reactions. The application of high-pressure extends the thermodynamic conditions to high temperature not attainable in ‘open’ systems. Owing to the confined reaction space, the entropy of the system can be increased in a controlled manner to the stage, when the substrates are dissolved at high concentrations, well mixed, and their molecules excited into high E_p conformers, high vibrational states and dissociated. Then by lowering temperature the high-entropy nucleation and subsequent kinetic crystallization can overcome the thermodynamic equilibrium and result in the high yields of

exchanged disulphides without catalyst required for ambient-pressure reactions. The comprehensive studies, utilizing DIP-MS, NMR, TG-DSC, single-crystal and powder diffraction and theoretical calculations, corroborate this mechanism and understanding of the disulphide exchange reactions. The application of high-pressure is essential for the high-entropy effects (including the excited conformational states, S-S bond cleavage), the nucleation and subsequent kinetic crystallization, which are the key elements leading to the non-catalytic disulphide exchange. These results indicate the high-pressure techniques as most suited for tailoring a one-pot, high-yield reaction systems leading to high-quality single crystalline products. It can be noted that the pressure of about 0.2 GPa proved sufficient for sealing the reaction space is technologically well accessible in various types of equipment, for example in the lower range of operation of many piston-and-cylinder devices and in many autoclaves. At the same time the high-entropy methods eliminate the catalyst, which apart from the environmental issues including further purification of obtained product, make them financially competitive.

ASSOCIATED CONTENT

In detail description of all experimental data, including high-pressure equipment, used analytic methods, volume calculations, as well as the summarized results, with all NMR and DIP-MS spectra, of all conducted high-pressure reactions in DAC and in compressed-mixtures reactions, description regarding deconvolution of the accompanying effect of temperature and non-hydrostatic pressure acting alone, details about molecular volume calculations and tabularized results, detailed crystallographic data of novel substrates and products and synthetic procedure for **10** is available free of charge via the Internet at <http://pubs.acs.org>.

The CIF files have been deposited in Cambridge Structural Database (CCDC, www.ccdc.cam.ac.uk) as supplementary publications with reference numbers 2033598-2033603 for synthesized heterodimers **3-10**, **10-12**, **13-12**, **3-9**, **5-13**, **5-10** and 2033604-2033606 for **15**, **6** and **10**, respectively.

AUTHOR INFORMATION

Corresponding Author

*szymon.sobczak@amu.edu.pl
*katran@amu.edu.pl

Author Contributions

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ABBREVIATIONS

DCC, dynamic covalent chemistry; DAC, diamond anvil cell; EWG, EDG electron donating or withdrawing group; DIP-MS, direct insertion probe – mass spectrometry.

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