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Combinatorial Chemistry | *Hot Paper*

Dithioacetal Exchange: A New Reversible Reaction for Dynamic Combinatorial Chemistry

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Abstract: Reversibility of dithioacetal bond formation is reported under acidic mild conditions. Its utility for dynamic combinatorial chemistry was explored by combining it with orthogonal disulfide exchange. In such a setup, thiols are positioned at the intersection of both chemistries, constituting a connecting node between temporally separated networks.

Dynamic combinatorial chemistry (DCC) has emerged as a strategy aimed at combining molecular diversity generation, self-selection of host–guest pairs, and purification in one pot.[1] Nowadays, applications of DCC range from molecular recognition,[2] catalysis,[3] and transport processes,[4] to the design of molecular walkers,[5] sensors,[6] and materials.[7] Interestingly, the new vision of systems chemistry has emerged as an extension of DCC and related areas.[8] DCC is based on the use of dynamic covalent bonds for the generation of a mixture of interconverting compounds. It is desirable that the reversible reactions involved in the preparation of such mixtures are reasonably fast, tolerant to a variety of functional groups, active under mild conditions, and susceptible to deactivation.[1c,d] Recent examples include orthoester exchange,[9] diselenide exchange,[10] and reversible native chemical ligation.[11] Reversible reactions involving aldehydes[12,13] or thiols[10b,14] have shown to be useful in DCC. In recent years, the scope of reversible reactions has broadened to include the addition of a thiol to an aldehyde, as described for thiazolidine exchange[15] and hemithioacetal formation.[16] Chemically related to them, the dithioacetal functional group has been widely used in organic synthesis as a precursor of acyl carbanion equivalents,[17] Lewis acid induced electrophiles,[18] and as a protective group for carbonyl compounds.[19] Acidic catalysis and temperature has enabled the reversible formation of dithioacetals from an aldehyde and a thiol[20] or the dithioketal exchange from a derivative of griseofulvin and thiols.[21] Milder conditions under basic catalysis were reported for the reversible formation or exchange of dithiano compounds from a thiol and a vinyl sulfide carbonyl or a β-dithiane carbonyl, respectively.[22]

In this work, we describe the reversible formation and exchange of dithioacetals under acidic conditions. Additionally, to evaluate the utility of the dithioacetal exchange in DCC, a double-level system was prepared by combining it with disulfide exchange. Initially dithioacetal formation was investigated by HPLC in a chloroform solution containing 3,4,5-trimethoxybenzaldehyde **A** (3 mM), 2-phenylethanethiol **1** (6 mM), and trifluoroacetic acid (TFA; 60 mM). After 3 h, a new compound could be observed by HPLC corresponding to the dithioacetal **1-A-1** (Figure 1).

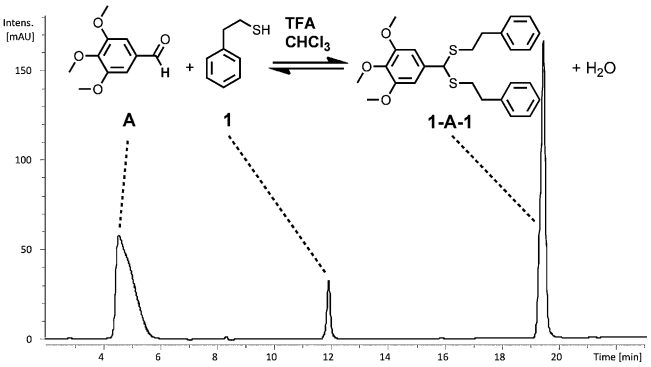

Figure 1. HPLC trace showing the composition achieved by starting from **A** and **1** ($\lambda = 265$ nm).

After 20 h of stirring, the composition remained without changes, ^{1}H NMR spectroscopy showed that **1-A-1** constituted 86% of the mixture composition, whereas both **A** and **1** were present in 14%.[23] When a chloroform solution of **1-A-1** (3 mM), H_2O (3 mM) and TFA (20 mM) was stirred for 2 h, the reached composition was the same than that observed in Figure 1 (see the Supporting Information, Figure S6), indicating the reversibility of the dithioacetal bond formation. Additionally, when chloroform solutions of **A** and **1**, or of **1-A-1** and H_2O (3 mM final concentration in all cases) were stirred in neutral (without TFA) or basic conditions (with piperidine 15 mM), the starting material remained unaltered after one week, indicating that both formation and hydrolysis of dithioacetals are inactive under those conditions.

To evaluate the reversibility of the exchange of dithioacetals, the compound **1-A-1** (3 mM final concentration) and *p*-thiocresol **2** (6.3 mM) were dissolved in a $CHCl_3$:TFA (95:5) solution

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and stirred for 3 h, then dithioacetal **3-A-3** (3 mM) was added. ^{1}H NMR signals ($\delta = 4.56–5.24$ ppm) corresponding to dithioacetal protons indicated the formation of the six expected dithioacetals (Figure 2).

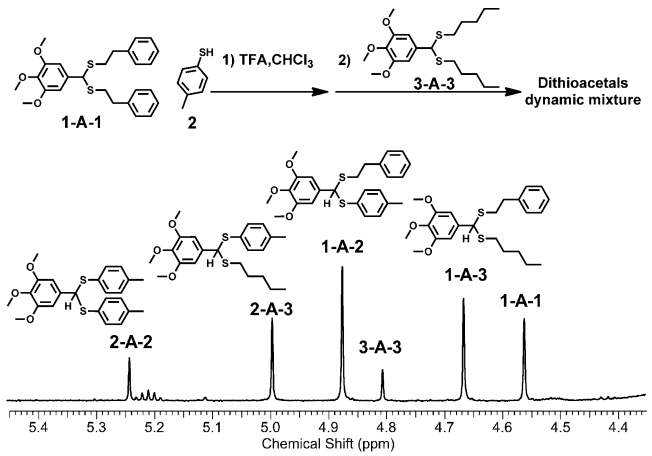

Figure 2. Partial ^{1}H NMR spectrum of the dynamic mixture prepared from **1-A-1**, *p*-thiocresol **2**, and then adding **3-A-3** in acid conditions.

At 14 h, the proportion of dithioacetals ranged between 6 and 20%, whereas the free aldehyde **A** was present in 28% of the total composition. This profile of composition remained unchanged up to two days of reaction, suggesting that equilibrium has been reached. In order to confirm it, the same mixture was prepared from a different starting point: a $CHCl_3$/TFA (95:5) solution of **2-A-2** and 1-pentanethiol **3** was stirred for 2 h and subsequently, **1-A-1** was added. As expected the composition at 14 h was the same as in the previous experiment and stayed constant up to two days, indicating that the mixture is under thermodynamic control (Figure S16 in the Supporting Information).[24]

Different reversible exchange reactions have been combined to prepare dynamic mixtures.[25] Some of them have been used to produce complex structures and functional systems.[26] One of the most widespread combinations makes use of orthogonal hydrazone and disulfide exchanges, which can be sequentially addressable.[27] We wonder if dithioacetal exchange could be used to prepare a multilevel system by combining dithioacetal exchange with orthogonal disulfide exchange. The construction of one dynamic system using two sequential reversible reactions can be conducted through two different sequences of activation. With this aim, a solution of dithioacetal **3-A-3** (2.7 mM), benzene disulfide **4-4** (2.7 mM), and 2-phenylethanethiol **1** (5.4 mM) in $CHCl_3$ was treated with TFA and then with piperidine in excess or, alternatively, first with piperidine and later with TFA. When TFA was added first (54 mM final concentration), only dithioacetal exchange took place: dithioacetals **1-A-1** and **1-A-3** were produced at the expense of **1** and **3-A-3** (Figure 3, *Path a*).[28] The concentration of benzene disulfide **4-4** did not change over a period of two days, indicating that the disulfide exchange is turned off. At that moment, an excess of piperidine was added (67.5 mM) leading to the formation of disulfides **1-4**, **1-1**, and **3-4**, and of benzenethiol **4** at the expense of **4-4**. Over a three-day period, the previous concentration of dithioacetals **1-A-1**, **3-A-3**, and **1-A-3** stayed constant, suggesting that the exchange of dithioacetals is turned off (Figure 3, *Path a*). At this moment, three dithioacetals, two thiols, and four disulfides were present in the solution. In the experiment following the opposite sequence, when piperidine

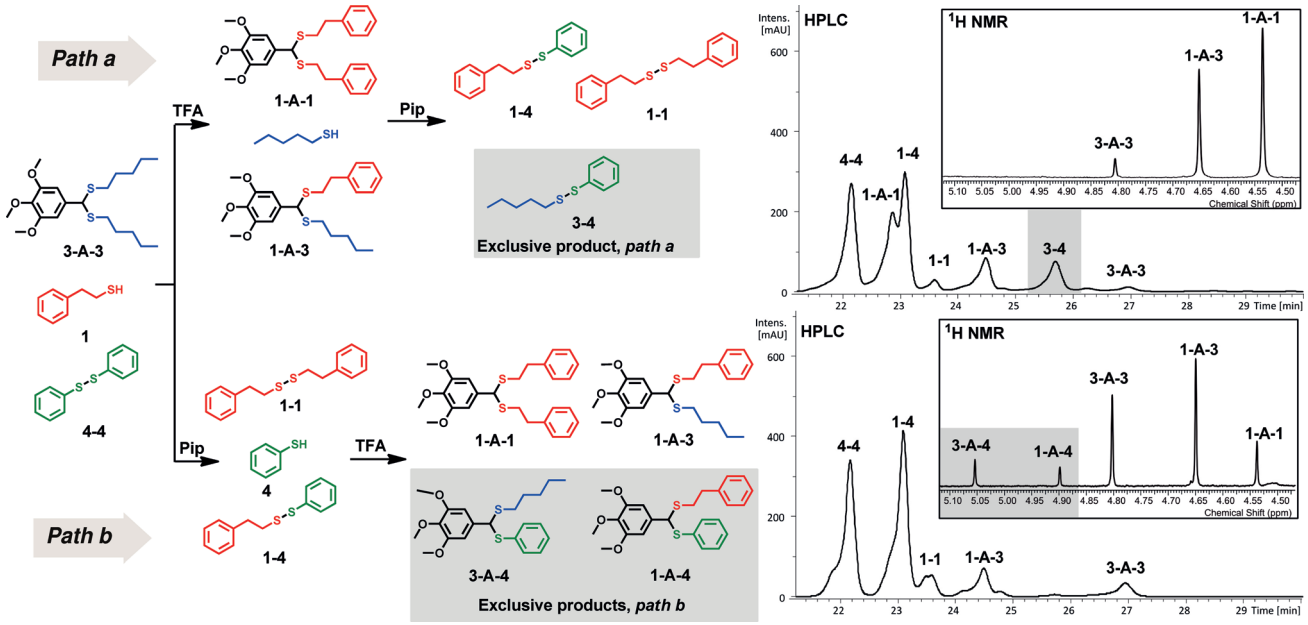

Figure 3. HPLC profile ($\lambda = 250$ nm) of a solution of dithioacetal **3-A-3**, disulfide **4-4**, and thiol **1** in $CHCl_3$ after the addition of TFA (2 days), followed by the addition of piperidine (2 days; *Path a*), or first piperidine (2 days) and then TFA (6 h; *Path b*). Inserts are partial ^{1}H NMR spectra showing dithioacetal protons for each mixture.

(13.5 mM) was added in the first instance to the solution, benzenethiol **4** and disulfides **1-4** and **1-1** were formed at the expense of **4-4** (Figure 3, *Path b*). As expected, stirring for two days under these conditions did not affect the concentration of dithioacetal **3-A-3**; and further addition of an excess of TFA (67.5 mM) led to the formation of dithioacetals **1-A-1**, **1-A-3**, **3-A-4** and **1-A-4** at the expense of **3-A-3**, with no effect on the concentration of the previously generated disulfides (Figure 3, *Path b*). At that moment, five dithioacetals, two thiols, and three disulfides were present in the solution. In summary, two different dynamic mixtures were obtained after each orthogonal process was completed (first acid then base or vice versa). These dynamic mixtures are constituted by a different range of disulfides and dithioacetals because different reactive species are present for exchange when the order of activation is changed. For example, dithioacetal **3-A-3** is exchanged only with **1** when the acid is added first, whereas, when the base was added first and then the acid, it is exchanged with **4**, released from the disulfide partner, and exchanged with **1**. In the context of networks, the thiols present in these mixtures can be deemed common nodes connecting two temporally separated molecular networks. Interestingly, thiols can detect the components of the active network, bringing information from one network to the other. Furthermore, since these two final systems have different chemical compositions, these common nodes are useful to design non-commutative complex chemical systems.[29]

Double-level systems can be classified according to the relative functioning of the exchanges as simultaneous or sequential. Additionally, they can be communicating, when both exchange processes share one or more reactive functional groups, or non-communicating when all the reactive functional groups involved in each exchange process are different. Up to now, combination of sequential exchanges has been based on the use of non-communicating exchanges such as hydrazones and disulfides.[27] In this work we complete the palette of combinations by reporting an example where thiols are involved in two sequential communicating levels. Boolean logic functions can be envisaged with such a combination of exchanges and functional groups to design and implement reaction logic and computation in double-level systems.[8c,16b]

This work shows the feasibility of using dithioacetal exchange as a useful tool for DCC, its compatibility with disulfide exchange, and how the combination of these exchange reactions can give unique properties for their use in systems chemistry.

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Keywords: dithioacetal exchange · dynamic combinatorial chemistry · reversible reaction · systems chemistry

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[24] Dithioacetal exchange was also observed when the 3,4,5-trimethoxyphenyl moiety in dithioacetal **2-A-2** was changed by a phenyl moiety (see the Supporting Information, section 4.1.).

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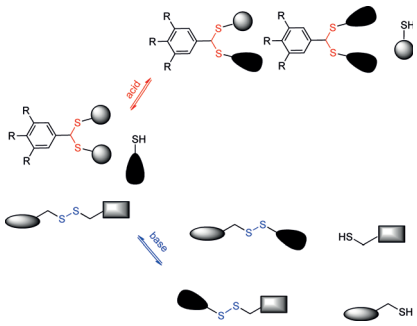
In reverse: Reversibility of dithioacetal bond formation is reported under acidic mild conditions (see figure). Its utility for dynamic combinatorial chemistry was explored by combining it with orthogonal disulfide exchange. In such a setup, thiols are positioned at the intersection of both chemistries, constituting a connecting node between temporally separated networks.



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