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Rewiring chemical networks based on dynamic dithioacetal and disulfide bonds

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Abstract

The control of the connectivity between nodes of synthetic networks is still largely unexplored. To address this point we take advantage of a simple dynamic chemical system with two exchange levels that are mutually connected and can be activated simultaneously or sequentially. Dithioacetals and disulfides can be exchanged simultaneously under UV light in the presence of a sensitizer. Crossover reactions between both exchange processes produce a fully connected chemical network. On the other hand, the use of acid, base or UV light connects different nodes allowing network rewiring.

Systems Chemistry aims to develop molecular systems of interacting and/or interconverting molecules that show emergent properties.[1] The field is nowadays learnig the design rules, mastering the underlying basic chemistry, and developing analytical tools to design new emergent behaviors.[1a]

The preparation of complex reaction networks constitutes an important part of systems chemistry.[2] One of the more successful methods to generate reaction networks is dynamic combinatorial chemistry[1c,3] wherein a few small building blocks react reversibly with each other, giving rise to mixtures of library members or dynamic combinatorial libraries (Figure 1). In this context, appropriate control of the reversible chemistry used to interconvert library members can rewire the network by addition or removal of connections betweeen nodes, changing both, the structure of the molecular network and the system adaptability towards environmental changes.[4]

Covalent dynamic combinatorial chemistry usually utilizes one type of dynamic covalent bond to generate molecular diversity. The combination of more than one type of reversible chemistry in the same system adds complexity layers and offers additional handles to control it. However, exploitation[5] and exploration of dynamic chemical systems constructed by using two,[6] three[7] or more[8] reversible covalent chemistries are still scarce.

In terms of connectivity, combined reversible chemistries can be orthogonal, when each functional group is involved in the formation of only one type of covalent bond, or they can communicate to each other, which means that some of the functional groups can form more than one type of covalent bond. In addition, orthogonal and communicating reversible reactions can be simultaneously or sequentially activated. Combining simultaneous exchange chemistries that can communicate leads to the generation of two exchange pools that share a building block type; consequently, any increase of the amount of this building block type in one pool depletes it in the other one leading to antiparallel chemistries.[9]

Recently, we introduced the use of dithioacetals in dynamic covalent chemistry.[10] Dithioacetals can be exchanged under acidic conditions, are stable in neutral and basic conditions, and their concentration can respond to templates.[11] Dithioacetals share the thiol building block with disulfides, one of the most popular dynamic covalent bonds,[12] so both reactions can communicate. Interestingly, each of these two exchange processes can be activated individually in organic solvents using appropriate acid/base conditions.[10] When combined in one single dynamic system, these two reactions allow the chemical communication between two diversity layers that can be sequentially activated. In addition to nodes and edges used to describe “monolayer” molecular networks,[13] the network of this system has two layers of complexity. Multilayer networks are networks of networks equipped with intra- and inter-layer edges.[14] As a consequence, each network is interconnected to and interdependent with another network.

Although dynamic disulfide bonds are normally activated under basic conditions,[12d] they can also be elicited in the presence of phosphine-[15] or NHC-based[16] catalysts as well as under ultrasound,[17] grinding[18] and photoirradiation.[19] The photochemical exchange of dithioacetals has not been

explored, however the photoactivation of their C-S bond has been exploited for addition of dithioacetals to alkenes[20] and for deprotection of dithioacetals.[21] Here we report that: (a) dithioacetals can be exchanged under UV light in the presence of a sensitizer, (b) disulfides can be exchanged under the same conditions, (c) crossover reactions occur under photochemical conditions when disulfides and dithioacetals coexist in the same system, and (d) the use of acid, base or UV ligth changes nodes connectivity. In this way the network can be rewired to selectively access the disulfides or the dithioacetals layer, or to access the whole chemical network (Figure 1).

The exchange of dithioacetals **1A1** and **2A2** (Figure 2a,b) was initially attempted under a series of photochemical conditions varying the amount of photosensitizer, atmosphere, solvent, volume, mode of stirring and dithioacetal concentration (see Section 4.1.1. in Supplementary Information). The best results were obtained in an oxygen-saturated acetonitrile-d_3 solution containing the two starting dithioacetals (30 mM) in the presence of 9,10-dicyanoanthracene (DCA, 0.3 mM) as a photosensitizer. Light exposure (λ = 365 nm) of the stirred solution led to a constant concentration of the heterodithioacetal product **1A2** (Figure 2c) after 5 h of reaction. At this moment, the mixture was equilibrated (Figure 2d). When the reaction was carried out starting from dithioacetals derived from different thiols and aldehydes, a statistical distribution of dithioacetals is achieved in around ten hours (Figure S1).

It has been reported that dithioacetals can form radical species under irradiation in similar conditions.[20,21b,21d,22] Therefore, the time evolution of the reaction was monitored by HPLC in the presence of TEMPO. Mixtures of **1A1** and **2A2** were exposed to UV light, and TEMPO was added at different times (Figure 3). Inhibition of the exchange reaction suggests that the photosensitized dithioacetal exchange requires radical intermediary species.

Then the simultaneous activation of disulfide and dithioacetal exchanges was studied. With this aim, the exchange of disulfides was attempted under the photochemical conditions previously used for the exchange of dithioacetals. A solution of disulfides **11** and **22** (Figure 4a,b) was exposed to UV light/DCA giving place to the exchange product **12** (Figure 4c), which reached a steady concentration after 3 h of reaction (Figure 4d).[23]

The existence of crossover between disulfides and dithioacetals exchanges under photochemical conditions was analyzed next. Exposure of disulfide **11** and dithioacetal **2A2** to UV-light led to the expected disulfides, **12** and **22**, and dithioacetals, **1A1** and **1A2** (Figure 5a-c). Formation of the disulfide product **12** was the fastest, reaching a constant concentration in 4 h (Figure 5d,e).[23] This crossover experiment shows that the formation of heteroproducts **12** and **1A2** (Figure 5d,e) is slower than in the experiments based on isolated dithioacetals or disulfides exchanges (Figures 2d and 4d, respectively), indicating that building block transference between two dithioacetals or between two disulfides is faster than the crossed transference between one dithioacetal and one disulfide. This could be the result of limited building block availability, which is regulated by a decreased reactivity of one particular functional group. For instance, the slower formation of disulfide **12** in this experiment

could be due to a decreased reactivity of dithioacetals **1A2** and **2A2**, who are the only source of building block **2** able to produce **12**. Alternatively, the two exchange processes could affect their kinetics by sharing one common reagent or intermediate that can act as a hub of the network.[24]

In order to explore further the disulfide/dithioacetal crossover, a system was studied in which building blocks **1** and **2** are available independently of the other co-existing exchange process. Exposure of dithioacetals **1A1** and **2A2** and disulfides **11** and **22** to UV-light led to a constant concentration of the disulfide product **12** after 3 h of reaction, an almost identical behaviour to that of the isolated disulfide equilibrium (Figure 6a). This gives further support to dithioacetal controlled building block shortage as one cause for the delay observed in the previous experiment (shown in Figure 5). On the contrary, formation of dithioacetal **1A2** in the presence of disulfides was slower than in the isolated dithioacetal equilibrium, demanding about 40 h to reach a nearly constant dithioacetal ratio (Figure 6b). This result suggests that the observed differences are most likely due to different kinetics of the reactions between the formed radicals and the disulfides or the dithioacetals. In this case radical species would react faster with disulfides than with dithioacetals, so the disulfides exchange at more or less the same rate as in the isolated system, whereas the dithioacetals exchange slower than in the isolated system.

The study of reaction kinetics on dynamic chemical systems is gaining increasing attention.[25] Differences in reactivity between isolated and networked reversible reactions have been previously described by the group of Lehn for imine formation and exchange,[2a] showing that competition between different amino compounds may lead to out-of-equilibrium states where a slow formation step leads towards the equilibrium with a nonlinear kinetics. In other example, some simultaneous-communicating reactions have been showed to have a very slow velocity, impeding to exactly determine whether the equilibrium point has been reached.[7a]

Selective or dual activation of disulfide and dithioacetal exchange under acid/base/photochemical conditions can be used to network rewiring (Figure 1). Treatment of a static mixture of **11** and **2A2** with TEA and the thiol **2** selectively activates the disulfide layer of the network whereas the dithioacetal layer stays disconnected (Figure 7a). Addition of TFA disconnects the disulfide layer and activates the dithioacetal layer (Figure 7b). Sequential activation of exchanges results in a multilayer molecular network in which the layers are separated in activation time but connected through thiol nodes (Figure 7c). The two layers can be activated in the opposite sequence by adding first the corresponding thiol **1** and the acid and then the base (Figure 7d–f). The differences observed in the final compositions of these mixtures are the result of the systems history. In parallel, simultaneous photochemical activation of the disulfide and dithioacetal layers (Figure 7g) connects all the nodes sharing the same type of building block, leading to a fully wired network (Figure 7h).

Controlling relationships between nodes leads to an assortment of network structures. A change in network structure can have a significant effect on the responsiveness of the system. It represents an interesting entry point to analyze the effect of network structure on the function of fully reversible

covalent systems. Since each layer of the multilayer molecular network is dynamic, multiple responses can be expected for a given selective pressure. Given that different layers are not independent of each other, adaptation reached in the first level of exchange could, in theory, be transmitted to the next layer even when the selection pressure has disappeared. The connection of reversible processes to irreversible processes has been studied by the groups of Ramström,[2c,5d,26] Miljanić,[8,24,27] Herrmann[28] and Philp,[29] giving access to a variety of systems with interesting properties. The connection of reversible processes to other reversible processes that can be sequentially or simultaneously activated opens interesting possibilities, in particular in line with the antiparallel chemistry concept recently proposed by the group of Otto.[9] In this work, rewiring is introduced to engineer novel synthetic multi/monolayer networks in complex chemical systems.

Experimental Section

In a typical experiment, dithioacetals and/or disulfides (15 µmol of each one) were dissolved in acetonitrile (0.5 mL) containing DCA (0.03 mg, 0.15 µmol). The resulting solution was poured in a 5 mL test tube and oxygen was bubbled for 3 min before closing the system. The test tube was placed close to a UV desk lamp (4W, λ = 365 nm) and the solution was magnetically stirred (speed = 350 rpm). ^{1}H-NMR or HPLC-UV monitoring involved transferring the solution to a NMR tube or HPLC vial, make the measurement and then pour the solution back to the test tube or vial to extend the time of light exposure. For more details, see the Supporting Information.

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[23] The HPLC-UV peak area is proportional to the concentration of the different homo disulfides **11** and **22** and homo dithioacetals **1A1** and **2A2** in the concentration range tested (Supplementary information Figures S4-S11).

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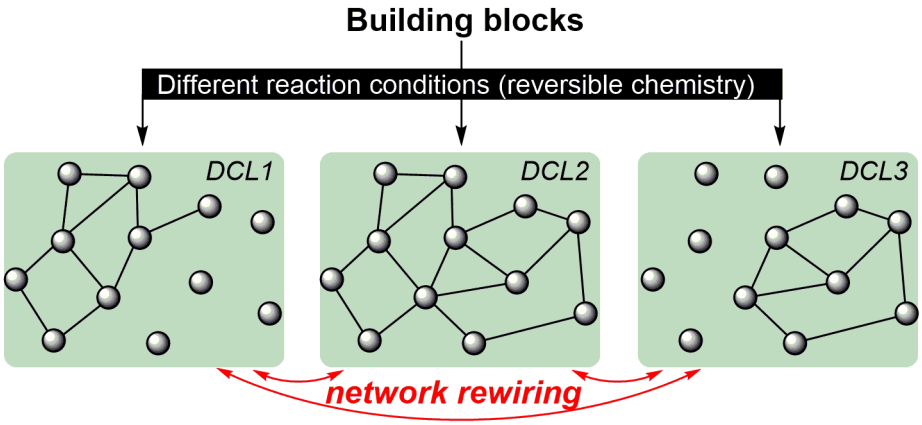

Figure 1. Network rewiring in dynamic combinatorial libraries (DCLs).

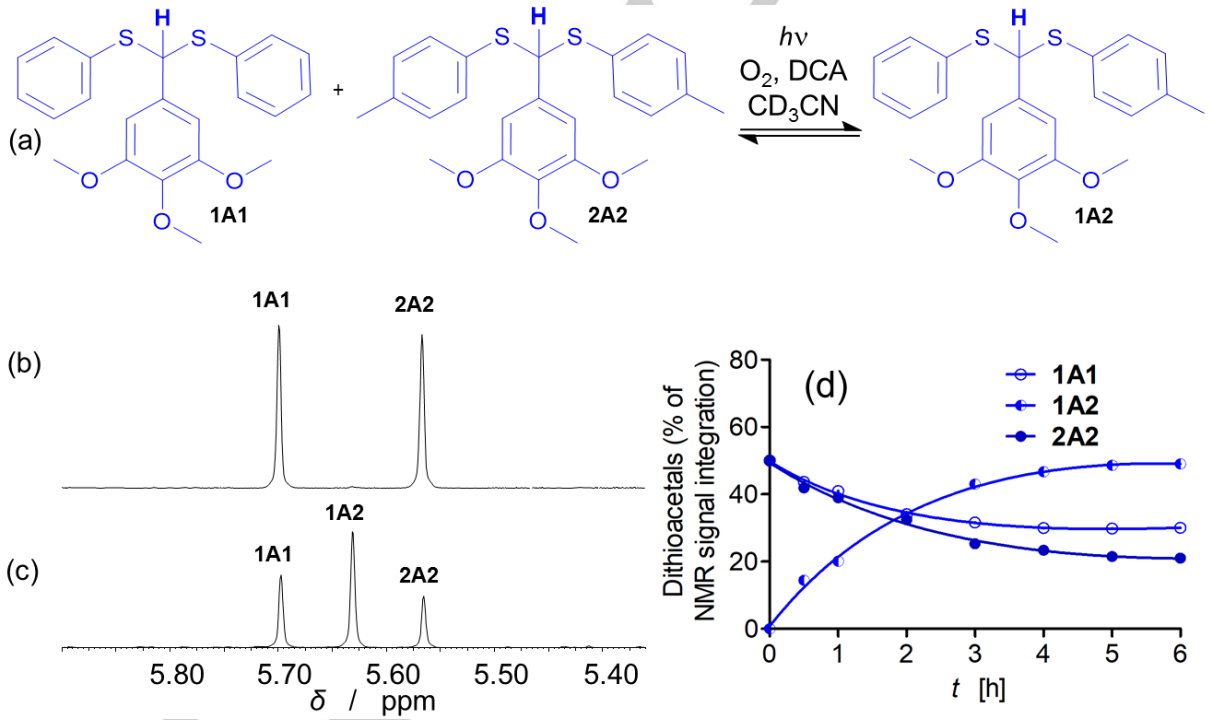

Figure 2. (a) Photochemical exchange (λ = 365 nm) of dithioacetals **1A1** and **2A2** (30 mM of each one) in an oxygen-saturated acetonitrile-d_3 solution in the presence of DCA (0.3 mM). Signals of the dithioacetal groups protons in the ^{1}H-NMR spectra (CD_3CN, 600 MHz, 298°*K*) recorded (b) before or (c) after 4 h of photoreaction. (d) Kinetic profile of the reaction. *Y*-axis shows the proportion of dithioacetals calculated from the integration of dithioacetal proton signal in the ^{1}H-NMR spectra expressed as percentage of the total integration for dithioacetal proton signals.

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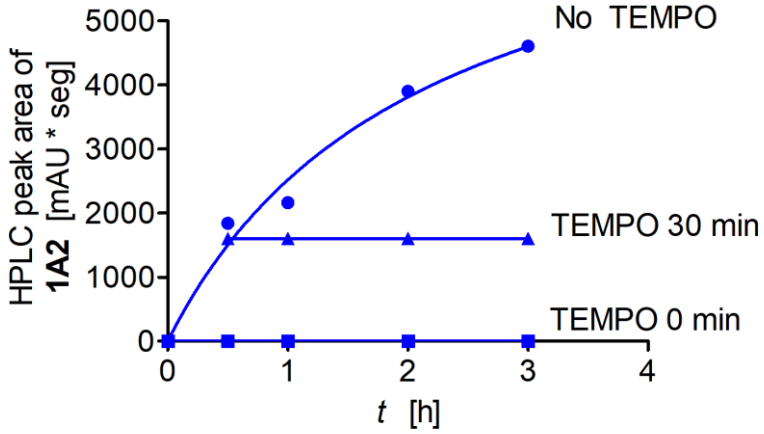

Figure 3. Effect of the addition of TEMPO on the dithioacetal exchange between **1A1** and **2A2** (30 mM of each one) in an acetonitrile solution saturated with O_2 and in the presence of DCA (0.3 mM). *Y*-axis shows the HPLC-UV peak area for dithioacetal **1A2** (λ = 250 nm)**.**

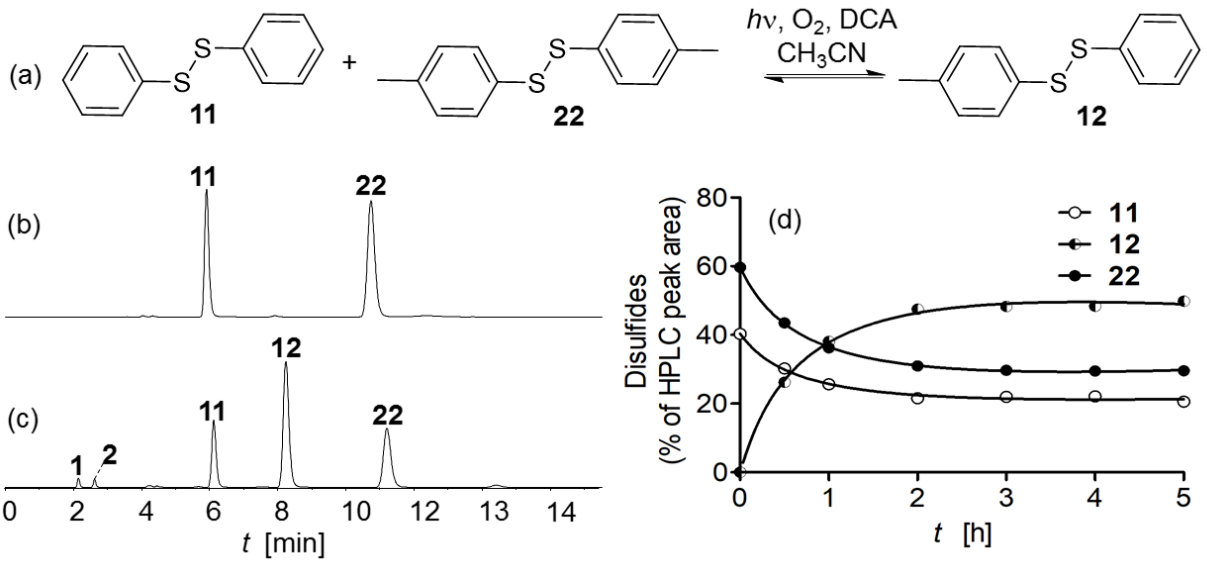

Figure 4. (a) Photochemical exchange (λ = 365 nm) of disulfides **11** and **22** (30 mM of each one) in an oxygen-saturated acetonitrile solution in the presence of DCA (0.3 mM). HPLC-UV chromatograms (λ = 250 nm) as obtained (b) before and (c) after 2 h of photoreaction. (d) Kinetic profile of the reaction. *Y*-axis shows the HPLC-UV peak area for disulfides **11**, **12** and **22** (λ = 250 nm) expressed as percentage of the total disulfide peaks area**.**

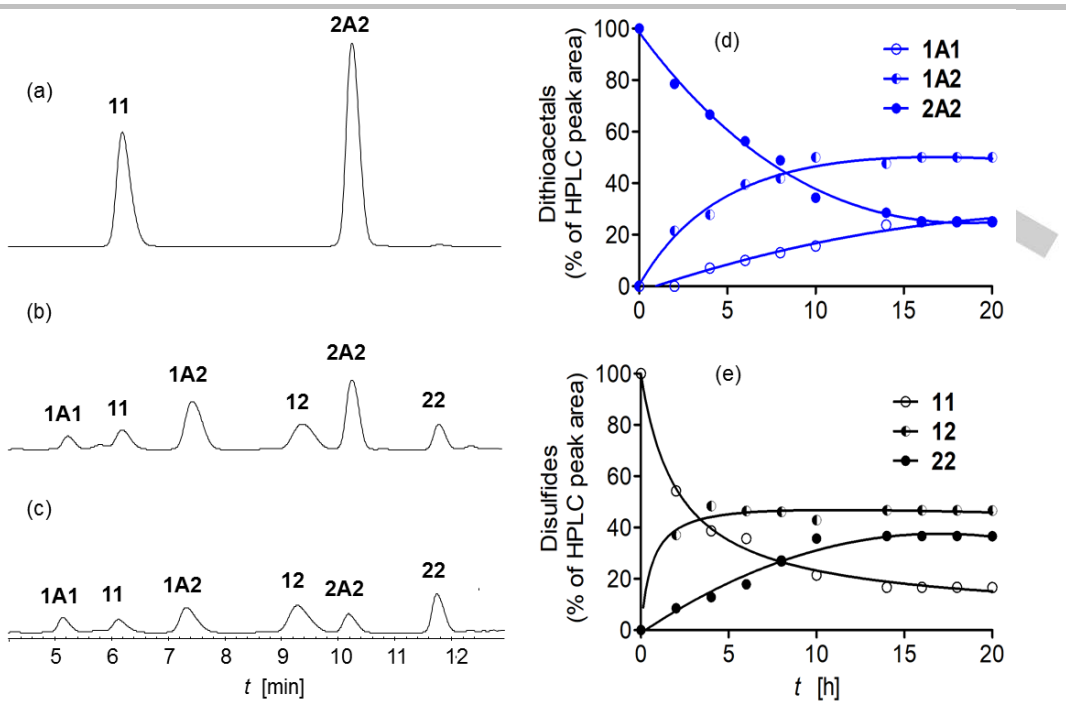

Figure 5. HPLC-UV chromatograms (λ = 250 nm) of the mixtures formed from **11** and **2A2** (30 mM of each one) in an oxygen-saturated acetonitrile solution with DCA (0.3 mM) as obtained (a) before or after (b) 8 h or (c) 14 h of photoreaction. Kinetics of the equilibration of (d) dithioacetals and (e) disulfides. *Y*-axis in (d) shows the HPLC-UV peak area for dithioacetals **1A1**, **1A2** and **2A2** expressed as percentage of the total dithioacetal peaks area**.** *Y*-axis in (e) shows the HPLC-UV peak area for disulfides **11**, **12** and **22** expressed as percentage of the total disulfide peaks area**.**

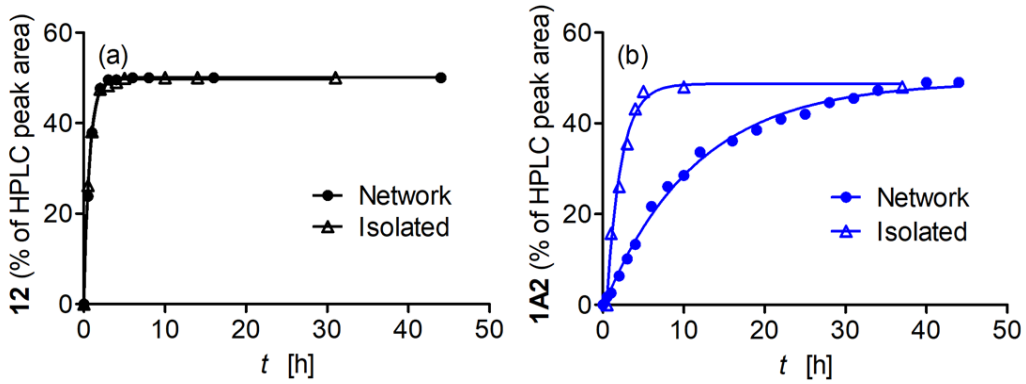

Figure 6. Comparison of the kinetic profiles of formation of **12** and **1A2** through isolated and networked disulfide and dithioacetal photochemical exchanges. In the "network" experiment (a and b) product formation results from the photochemical exchange (λ = 365 nm) of disulfides **11** and **22** (30 mM of each one) and dithioacetals **1A1** and **2A2** (30 mM of each one) in an oxygen-saturated acetonitrile solution in the presence of DCA (0.3 mM). The "isolated" disulfide experiment (a) is carried under the same conditions but in absence of dithioacetals. The "isolated" dithioacetal experiment (b) is carried out under the same conditions but in absence of disulfides. *Y*-axis shows the HPLC-UV peak area (λ = 250 nm) for disulfide **12** expressed as percentage of the total area of disulfide peaks (a), or for dithioacetal **1A2** expressed as percentage of the total area of dithioacetal peaks (b).

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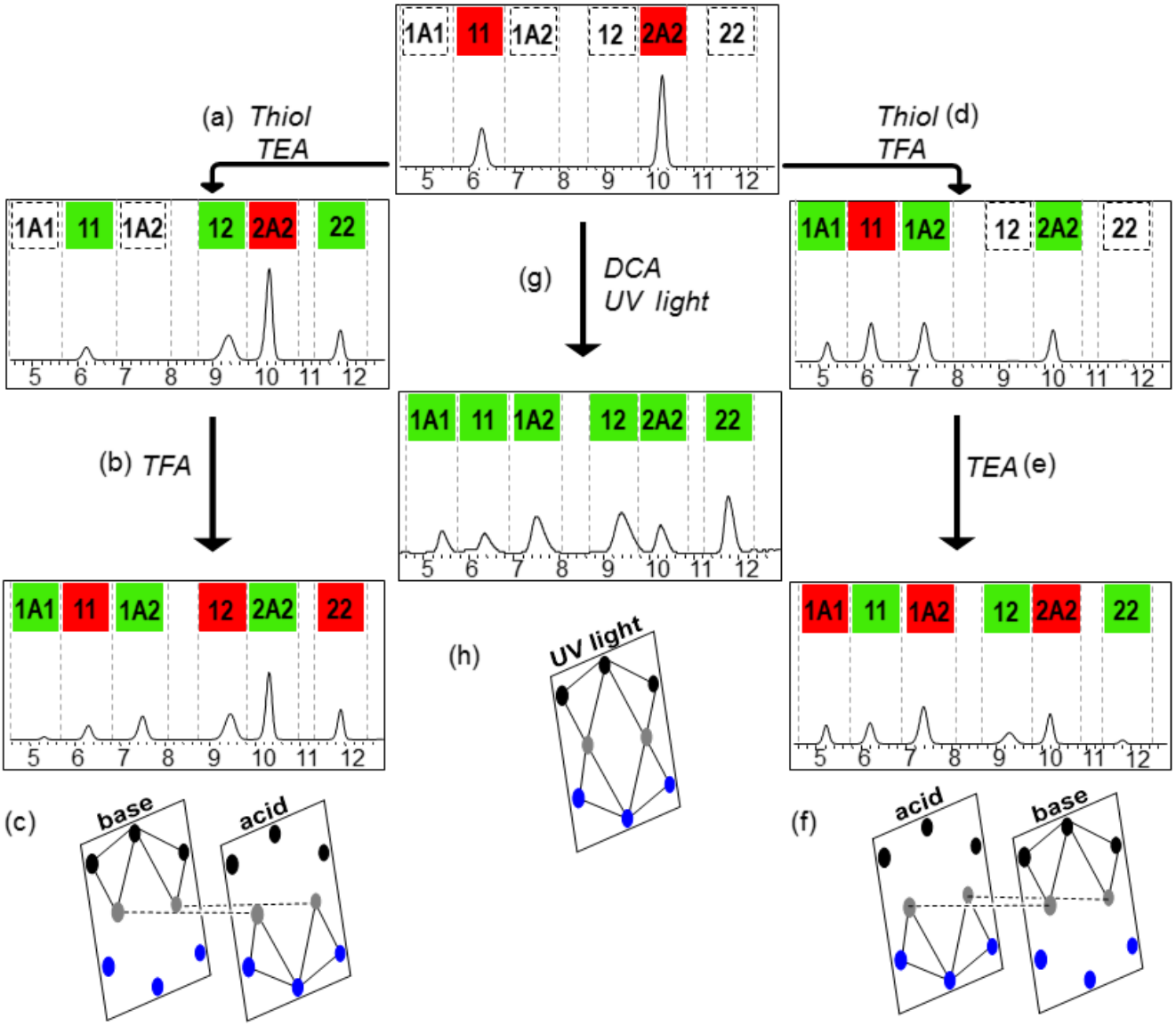

Figure 7. HPLC chromatograms obtained when the exchange of disulfide **11** and dithioacetal **2A2** was sequentially activated (a-b and d-e), leading to multilayer networks (c and f), or simultaneously activated (g) leading to a fully connected monolayer network (h). Chromatogram labels: components involved (green) or not involved (red) in a dynamic exchange process. Components that are formed under some of the other conditions used, but not under the conditions depicted (dotted). Network graph labels: disulfides (black), dithioacetals (blue). Grey nodes represent thiols under base and acid conditions (c and f) or radical species under UV light (h).