Dynamic Covalent Chemistry

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Complex Functional Systems with Three Different Types of Dynamic Covalent Bonds**

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Abstract: *Multicomponent surface architectures are introduced that operate with three different dynamic covalent bonds. Disulfide exchange under basic conditions accounts for the growth of π stacks on solid surfaces. Hydrazone exchange under acidic conditions is used to add a second coaxial string or stack, and boronic ester exchange under neutral conditions is used to co-align a third one. The newly introduced boronic ester exchange chemistry is compatible with stack and string exchange without interference from the orthogonal hydrazone and disulfide exchange. The functional relevance of surface architectures with three different dynamic covalent bonds is exemplified with the detection of polyphenol natural products, such as epigallocatechin gallate, in competition experiments with alizarin red. These results describe synthetic strategies to create functional systems of unprecedented sophistication with regard to dynamic covalent chemistry.*

Dynamic covalent bonds are fascinating because of their dual nature.[1,2] Under some conditions, they are as rapidly reversible as noncovalent bonds whereas under different conditions, they exist as irreversibly as covalent bonds. This dual nature is of key importance to build "living" functional systems that can self-sort, self-heal, adapt, template, amplify, exchange, replicate, transcribe, sense, walk, penetrate cells, and respond to a broad spectrum of physical and chemical stimuli, including light.[1,2] Synthetic methods that employ a single type of dynamic covalent bond to create function are very well developed.[1] In sharp contrast, only a few pioneering examples exist for two types of dynamic covalent bonds that work together.[2] Of these examples, the best developed is the combination of disulfide exchange under basic conditions and hydrazone exchange under acidic conditions.[2–6] Additional promising alternatives include boronic ester,[7–10] thioester,[11] amide,[11,12] imine[8,13–15] and hemiaminal exchange,[16] Michael adducts,[17] olefin metathesis,[15] and Cope rearrangements.[9] Functional systems that employ more than two organic dynamic covalent bonds together have not been reported. Attempts to also integrate inorganic coordination chemistry into systems with more than two dynamic covalent bonds have focused mostly on structural aspects.[18] The rare use of more than one organic dynamic covalent bond in concert is surprising because noncovalent bonds are routinely used together to build complex functional systems.[2] Herein we report multicomponent surface architectures that are built with three different types of dynamic covalent bonds.

The construction of multicomponent surface architectures with three different types of dynamic covalent bonds was based on the recently introduced SOSIP–TSE method (SOSIP = surface-initiated polymerization; TSE = templated stack exchange).[5,6] Oriented π stacks of naphthalenediimides (NDIs) were grown directly on indium tin oxide (ITO) surfaces by SOSIP. This established method operates with ring-opening disulfide-exchange chemistry under basic conditions. For simplicity, building blocks used for disulfide exchange were labelled with an **S**, hydrazone exchangers with **H**, boronic ester exchangers with **B**, and the resulting surface architectures as the respective combination (Figure 1). In architecture **S1H1** obtained by SOSIP,[5,6] the individual NDI stacks are separated by NDI templates on the surface and benzaldehyde templates **H1** along the stack. The substitution of **H1** in **S1H1** by hydrazone exchange under acidic conditions has been referred to as TSE (or string exchange in the absence of clear stacks).[5,6] TSE is a two-step process composed of templated stack or string release (TSR) followed by templated stack or string addition (TSA).

TSR of aldehyde **H1** from surface architectures **S1H1** was achieved by dipping the ITO electrodes in aqueous solutions of hydroxylamine (Figure 1).[5,6] The formation of surface architectures **S1** was followed by changes in the absorbance of the transparent ITO electrodes as described (see Figure S1 in the Supporting Information).[5,6] For TSA, the hydrazides produced along the NDI stacks in surface architecture **S1** were then reacted under acidic conditions with aldehydes containing an additional boronic acid, for example, **H2** or **H3**. According to changes in the absorbance of the ITO electrodes, TSE from **S1H1** to **S1H2** (or to **S1H3**, etc.) was general and occurred in quantitative yield (Figure S1). A focused screening of different boronic acids identified **H2** and the newly synthesized[19] formylated benzoboroxole or benzoxaborole[19] **H3** as the best. Among other boronic acids tested, the ones in the *ortho* position to aldehydes[7,8] did not perform as well, presumably because of unfavorable topology and direct dependence of boronic ester exchange on hydrazone exchange.

Boronic ester formation of alizarin red (**B1**)[20] in solution shifts the broad absorption maximum of the chromophore from $\lambda_{max} = 530$ nm to $\lambda_{max} = 460$ nm (Figure 2a). Apparent

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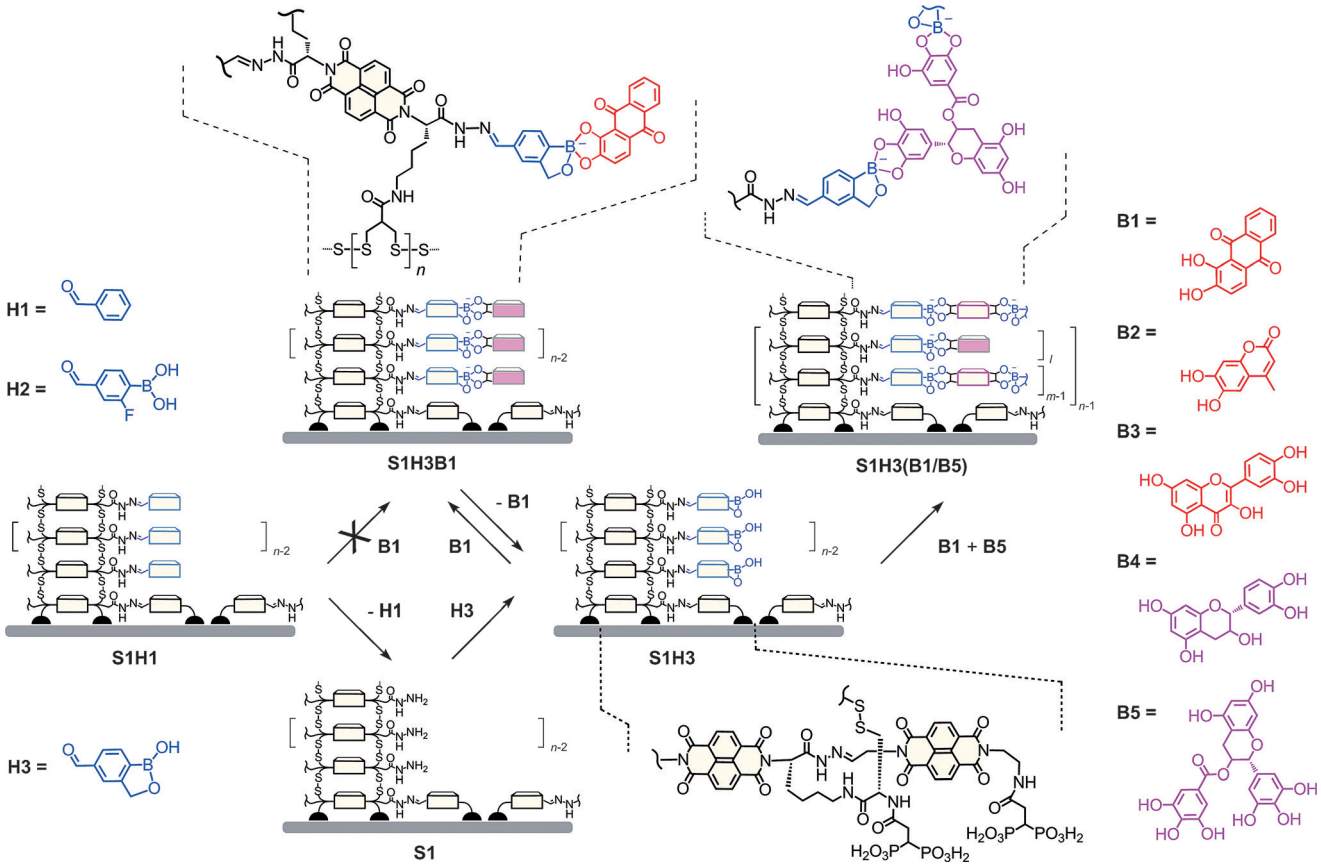

Figure 1. Structures of representative surface architectures **S1H3B1** and **S1H3(B1/B5)** with dynamic covalent disulfides, hydrazones, and boronic esters. The synthesis starting from **S1H1** and molecular structures of all hydrazone (**H1**–**H3**) and boronic ester exchangers (**B1**–**H5**) are shown.

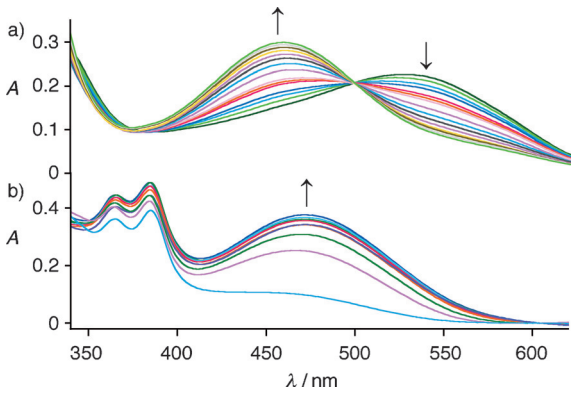

Figure 2. a) UV/Vis absorption spectra of **B1** (43 μM) in 75% MeOH, 100 mM HEPES, pH 7.8, in the presence of increasing concentrations of **H3** (0–50 mM). b) Absorption of **S1H3** after incubation with increasing concentrations of **B1** in DMSO (2% Hünig's base, 0.4–100 mM).

dissociation constants in MeOH/water 3:1 increased from **H3** ($K_D = 1.46$ mM) to **H2** ($K_D = 90$ μM; Table 1, entries 3 and 4). Incubation of **S1H3** with a solution of **B1** in DMSO containing Hünig's base (2%) afforded an ITO electrode with strong absorbance at $\lambda_{max} \approx 465$ nm (Figure 2b). Confirming the formation of boronic esters, the appearance of this band was consistent with the formation of **S1H3B1** (Figure 1).

Dose–response curves revealed that complete TSA to **S1H3** occurs with concentrations of **B1** down to approximately 3 mM (Figure 3a). The EC_{50}, that is the concentration needed to observe 50% of the maximal TSA, was found at $EC_{50} = 620$ μM (Table 1, entry 4).

The same dose–response curve gave a maximal yield $\eta_{MAX} = 92\%$ for the construction of **S1H3B1** (Figure 3a;

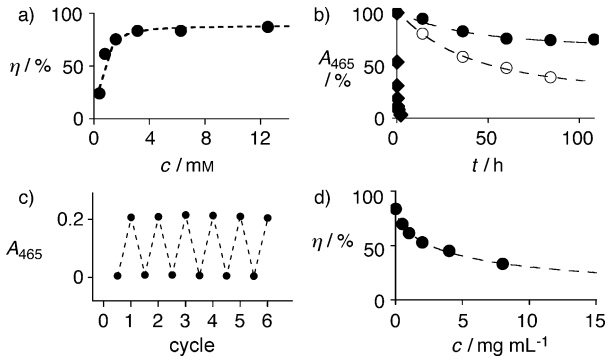

Figure 3. a) TSA yields for **S1H3B1** as a function of the concentration (*c*) of **B1** during incubation of **S1H3** in DMSO (2% Hünig's base; using data from Figure 2b with Hill analysis). b) Absorption at $\lambda = 465$ nm as a function of incubation time of **S1H3B1** in wet DMSO (◆), dry DMSO (○), and dry toluene (●). c) Reversibility of TSR from **S1H3B1** (see (b)) and TSA to **S1H3** (Figure 2b, with 100 mM **B1**). d) TSA yields for **S1H3B1** as a function of the concentration of **B6** during incubation of **S1H2** in DMSO (Hünig's base (2%), **B1** (3.1 mM); from Figure S17b).

Table 1: Characteristics of surface architectures.

	System[a]	η_{MAX} [%][b–e]	EC_{50} [mM][f–h]	K_D [mM][i]	t_{50} [s][j]
1	**S1H2**	99[b]	ca. 10	–	$>10^5$
2	**S1H1B1**	0[c]	–	–	–
3	**S1H2B1**	87[c]/49[d]	12[f]	0.09	976
4	**S1H3B1**	92[c]/44[d]	0.62[f]	1.46	233
5	**S1H2B2**	97[c]/34[d]	1.3[f]	0.03	201
6	**S1H3B2**	76[c]/35[d]	0.56[f]	4.20	43
7	**S1H2B3**	49[c]/17[d]	15[f]	0.17	65
8	**S1H3B3**	49[c]/22[d]	1.3[f]	1.04	27
9	**S1H3B4**	100[e]	76[g]/22[h]	-	–
10	**S1H3B5**	66[e]	4.6[g]/2.1[h]	–	–
11	**S1H3B6**	100[e]	–[g]/5.1[h]	–	–

[a] See Figure 1 for structures. [b–e] Maximum yields for TSA and TSE, estimated from dose–response curves based on changes in absorbance of the ITO electrodes (see, for example, Figures 2b and 3a). Comparison with the UV/Vis absorption spectra measured in solution after full destruction with mercaptoethanol indicated that, similar to the nearly environment-insensitive NDI absorption,[5,6] the extinction coefficients of the chromophores used to follow boronic ester exchange also do not change significantly in surface architectures. Hence, the accuracy of yields estimated directly from the absorbance of the ITO electrodes is reasonable. [b] TSE with hydrazones (4% AcOH).[5,6] [c] TSA in DMSO (2% Hünig's base). [d] TSA in 80% DMSO, pH 7.4. [e] From co-TSA with **B1**. [f–h] Half-maximal effective (EC_{50}) or inhibitory (IC_{50}) concentrations, that is, the concentrations needed to reach $\eta_{MAX}/2$. [f] EC_{50} value (mM; Figure 2b and 3a). [g] IC_{50} value for inhibition of **S1H3B1** (mM). [h] IC_{50} value for inhibition of **S1H3B1** (mg mL^{-1}; Figure 3d). [i] Dissociation constants of boronic esters **HxBx** in solution (75% MeOH, 100 mM HEPES, pH 7.8; Figure 2a). [j] Lifetime in wet DMSO (Figure 3b).

Table 1, entry 4). Control experiments showed that TSA of **B1** does not occur with **S1H1**, that is, in the absence of boronic acids (Figure 1; Figure S10, Table 1, entry 2). Controls also revealed that **S1H3** is not affected under these mildly basic conditions for the time needed for TSA, that is, disulfides and hydrazones remain intact during boronic ester exchange.

TSA of **B1** or coumarin[20] **B2** to **S1H2** or **S1H3** in DMSO with Hünig's base (2%) occurred with $\eta_{MAX} > 75\%$, whereas TSA in DMSO/water 8:2 gave $\eta_{MAX} = 34$–49% only (Table 1, entries 3–6; Figure S6–S9). Under the best conditions, TSA with quercetin (**B3**) gave only $\eta_{MAX} = 49\%$ for both **S1H2B3** and **S1H3B3** (Table 1, entries 7 and 8). This poor yield could indicate that **B3** forms esters with two proximal boronic acids in the confined space of the surface architectures (ongoing studies with multivalent chromophores strongly support this interpretation). For **B1**–**B3**, the EC_{50} values with **S1H3** were better than with **S1H2**, although K_D values with **H3** in solution were weaker than with **H2** (Table 1, entries 3–8). This finding confirmed previous observations[21] that the chemistry on surfaces, dominated by powerful proximity effects in confined space, and chemistry in solution are not the same. Further studies focused mostly on **S1H3** because of these impressive EC_{50} values.

With evidence for the generality of TSA by boronic ester formation in hand, TSE was explored next. TSR of **B1** from **S1H3B1** occurred spontaneously upon incubation in any solution containing water (Figure 3b). In wet DMSO, the half life (t_{50}) of the surface architectures increased from **S1H3Bx** to **S1H2Bx** (Table 1, entries 3–8; Figures S12, S13) and with increasing pH value (Figure S14, S15), that is, with the stability of the boronic ester. In dry DMSO, TSR rates became very slow (Figure 3b, Figure S16a). In dry toluene, surface architectures were stable for many days except for a minor initial decrease, possibly because of traces of water (Figure 3b, Figure S16b). TSR and TSA could be repeated without losses in yield simply by dipping **S1H3** into solutions with and without **B1**, that is, TSE by boronic ester exchange is unproblematic, also in the presence of disulfides and hydrazones (Figure 3c).

Co-TSA was explored by incubation of **S1H3** with increasing concentrations of catechin (**B4**) in DMSO containing Hünig's base (2%) and **B1** (3.1 mM). Decreasing absorption at $\lambda_{max} = 465$ nm was detected (Figure S17a). Dose–response curves gave an $IC_{50} = 76$ mM for the inhibition of **B1** addition by **B4**. This finding demonstrated that with increasing concentrations of **B4** at a constant concentration of **B1**, the composition of the produced surface architectures changes from red **S1H3B1** over mixed architectures **S1H3**(**B1**/**B4**) to the colorless **S1H3B4** (Table 1, entry 9). Complete inhibition of TSA of **B1** with **B4** at higher concentrations demonstrated that the synthesis of **S1H3B4** is quantitative ($\eta_{MAX} = 100\%$; Table 1, entry 9). For epigallocatechin gallate (**B5**), another major polyphenol in green tea, $IC_{50} = 4.6$ mM and $\eta_{MAX} = 66\%$ were found under the same conditions (Figure S17c; Table 1, entry 10). High activity and incomplete co-TSA were both consistent with the large size and the multivalency of **B5** (Figure 1).[7] Polyphenon 60 (**B6**), a commercially available green-tea extract, inhibited TSA of **B1** to **S1H3** with an $IC_{50} = 5.1$ mg mL^{-1} (Figure 3d; Table 1, entry 11). This intermediate activity was very meaningful considering that the weaker catechin (**B4**) and the stronger epigallocatechin gallate (**B5**) are the main polyphenols present in green tea. Compatibility of dose–response curves for polyphenon 60 with enzymatic signal generation for polyphenol sensing applications has been demonstrated previously in a different context.[7]

Taken together, these results demonstrate the existence and functional relevance of multicomponent architectures that operate with three different dynamic covalent bonds, namely disulfides, hydrazones, and boronic esters. Possible applications are diverse; directionality and compatibility with optoelectronic signal generation, transduction and detection, interfacing, and device fabrication appear particularly advantageous.[5–7,22,23] With regard to the development of synthetic methods, the next milestones will concern the integration of self-sorting[6b,c] and fully independent dynamics for three orthogonal dynamic covalent bonds, and the introduction of a fourth orthogonal dynamic covalent bond.

Keywords: boronic esters · dynamic covalent chemistry · hydrazones · multicomponent systems · supramolecular chemistry

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