Accelerating Hydrazone Exchange by UV Irradiation

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ABSTRACT Hydrazone exchange, a popular tool in systems chemistry, especially in dynamic combinatorial chemistry, suffers from relatively slow rates of equilibration, particularly when working with macrocyclic systems. This problem has been addressed by several different approaches, in general involving nucleophilic catalysis. In this report we present the application of UV irradiation to accelerate hydrazone exchange, using (*E*) - to (*Z*)-isomerization as the means of activating library members. A photostationary state was reached within one day, which, in the present system, resembled the state that took two weeks to reach in the absence of irradiation. This approach overcomes the use of excessive amounts of catalysts, working in forcing conditions, or the design of the systems being restricted to quickly exchanging species. It also broadens the connection between dynamic combinatorial chemistry and photochemistry, as photo-equilibration gives rise to photodynamic combinatorial libraries, an emerging phenomenon at the interface of these two chemistries.

Keywords: systems chemistry; dynamic combinatorial chemistry; hydrazone exchange; reversible covalent chemistry; photoswitching.

Introduction

Dynamic combinatorial chemistry (DCC) [1 – 14] studies mixtures of interconverting oligomers made of simple building blocks which reversibly connect through one or more types of covalent bonds, such as disulfide, imine, or (acyl) hydrazone linkages. Despite its relative novelty it has already established a prominent role in areas such as discovering molecular receptors [10, 15 – 18] and biologically active compounds [19 – 28], designing adaptive or responsive materials [2, 29 – 38], as well as in research on self-replicating molecules [39 – 46], complex reaction networks [47 – 54], and cascade reactions [55 – 56].

Acyl hydrazones are among the most exploited compounds in DCC due to their high stability, superior synthetic availability from the corresponding esters, and, more recently, because of the (photo)switchability of their C=N bonds [57 - 60].

However, they are also well-known for their often-sluggish formation and exchange, the latter particularly in macrocyclic systems, as the macrocyclic effect can act as a kinetic trap [61]. This problem has been approached by several different strategies [62], such as using extremely acidic environments (TFA in organic solvents) [9, 14], specifically designed building blocks [63 – 67], or often large amounts of nucleophilic catalysts [15, 61, 68 – 76] among which linear acyl hydrazides have proved to be particularly effective [61].

Aside from its use in the design of responsive materials [60, 77, 78] and reaction networks [79 – 81], as well as in creating diversity in dynamic combinatorial libraries (DCLs) [57, 82], the

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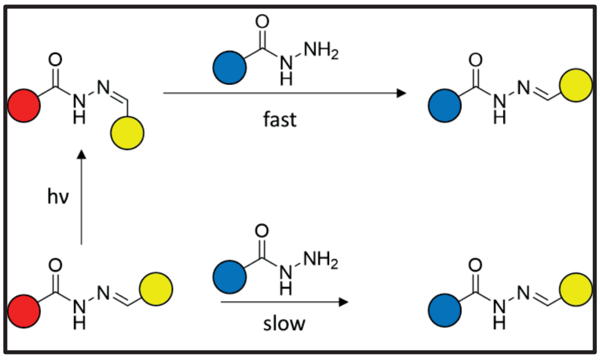
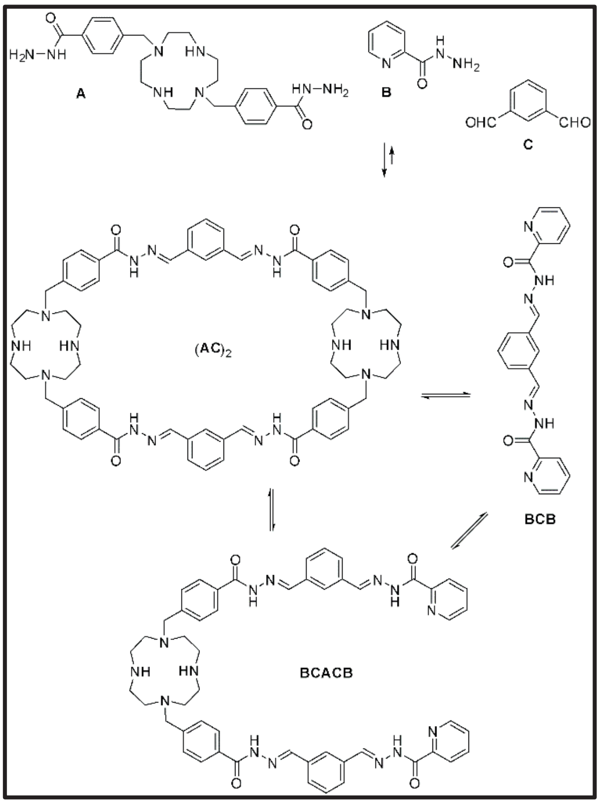
(photo)switchability of C=N bonds in hydrazones also offers a novel, fundamentally different approach to accelerate hydrazone exchange. Since the (*Z*)-isomers of hydrazones are generally less stable than the corresponding (*E*)-isomers, and hence likely to be more reactive, (*E*) → (*Z*)-photoisomerization can be expected to provide hydrazone-based DCLs with more reactive species (a similar approach has been applied with disulfide-based DCLs, but there the activated species are thiyl radicals [83], different molecular species). This should in turn lead to increased rates of hydrazone exchange (*Scheme 1*), especially in systems where the (*Z*)-isomers are not stabilized, *e.g.*, by intramolecular H-bonding. As it is not necessary that all hydrazones in a DCL have same the absorbance, UV irradiation of a DCL may ultimately lead not to an equilibrium, but, by selective activation, to a photodynamic [84 – 86] DCL. In photodynamic DCLs the composition is not controlled by thermodynamics, but rather by the kinetics of photoswitching and conversion of activated species into intermediate products and other library constituents. This characteristic makes such DCLs potentially interesting in the context of adaptive systems [47, 48, 50, 58 – 60]. However, photodynamic DCLs may have compositions close to equilibrated DCLs if the absorbances of the library constituents do not differ much. Thus, irradiation could be used to significantly shorten the period between the library setup and its equilibration.



Scheme 1. UV-catalyzed hydrazone exchange. The (*Z*)-isomer (*above*), produced by photoisomerization of a slowly reacting (*E*)-acyl hydrazone (*below*), is more reactive, which results in an increased rate of hydrazone exchange.

We tested the effects of UV irradiation on the exchange rates in acyl hydrazone libraries using a system comprising linear and macrocyclic hydrazones based on dihydrazide **A**, monohydrazide **B**, and dialdehyde **C** (*Scheme 2*). In this system several different species can be expected. **A** and **C** can give rise to a series of $(\mathbf{AC})_n$ macrocycles (*e.g.*, the $(\mathbf{AC})_2$ tetramer is shown in *Scheme 2*), **B** and **C** can form the **BCB** trimer (*Scheme 2*), while all three building blocks combined can yield a series of linear oligomers with general formula $\mathbf{BC(AC)}_n\mathbf{B}$ (**BCACB** is shown in *Scheme 2*). Mixing solutions of $(\mathbf{AC})_n$ macrocycles with **B**, as well as mixing solutions of **BCB** trimer with **A**, gives solutions in which all three building blocks are present, but condensed into hydrazones in different non-equilibrium states. If the overall concentrations of all three



Scheme 2. Building-block structures. Cyclen-based dihydrazide **A,** picolyl hydrazide **B**, and isophthalaldehyde **C**, and representative members of the DCLs: $(\mathbf{AC})_2$ tetramer, **BCB** trimer, and the **BCACB** pentamer.

building block units are the same in the starting solutions, their equilibration should lead to the same final composition. This principle could be used to assess whether the solutions have indeed reached equilibrium. The same principle, provided that thermal (*Z*) → (*E*) *i*somerization is quick, should hold when the solutions are exposed to UV, as the only expected photochemical reaction is the reversible (*E*) → (*Z*) photoisomerization. Hence, comparing the compositions of irradiated and non-irradiated solutions over time should tell whether UV-irradiation can be used to accelerate hydrazone exchange, *i.e.*, whether it leads to a composition similar to the one in an equilibrated system.

Results and Discussion

Prior to the UV irradiation experiments, we prepared and characterized the hydrazones formed from **A** and **C**, **B** and **C**, as well as the mixed library formed from **A**, **B**, and **C**. All hydrazones were prepared in aqueous ammonium acetate buffer (50 mM, pH 4.0), by mixing stock solutions of the corresponding hydrazide(s) and the aldehyde, with a final concentration of hydrazide and aldehyde groups of 2.0 mM. Characterization was performed by UPLC-MS, using the mixed DCL, and monitoring of equilibrating solutions was performed by UPLC. Upon mixing, **A** and **C** (solution (**A**, **C**)) initially formed a series of macrocycles which later equilibrated into predominantly $(\mathbf{AC})_2$ tetramer (*Figure 1*, *a*), while **B** and **C** (solution (**B**, **C**)) formed the **BCB** trimer, with a small portion of the unsaturated **BC** dimer and free hydrazide B (*Figure 1*, *b*). When all three building blocks were present (solution (**A**, **B**, **C**), *Figure 1*, *c*), along with the $(\mathbf{AC})_2$ tetramer and **BCB** trimer, a number of intermediate species was found, such as **BCACB**, $\mathbf{BC(AC)_2B}$, and $\mathbf{BC(AC)_3B}$, as well as several unsaturated species, such as **BCA**, **BCAC**, $\mathbf{BC(AC)_2}$, and $\mathbf{BC(AC)_3}$. Due to the large number of species in the DCLs (*Figures S1 - S22*), and the consequent overlapping of the peaks in the chromatograms, only the four major species: $(\mathbf{AC})_2$, **BCB**, **BCACB**, and $\mathbf{BC(AC)_2B}$, were used to monitor the composition of the DCLs during the experiments.

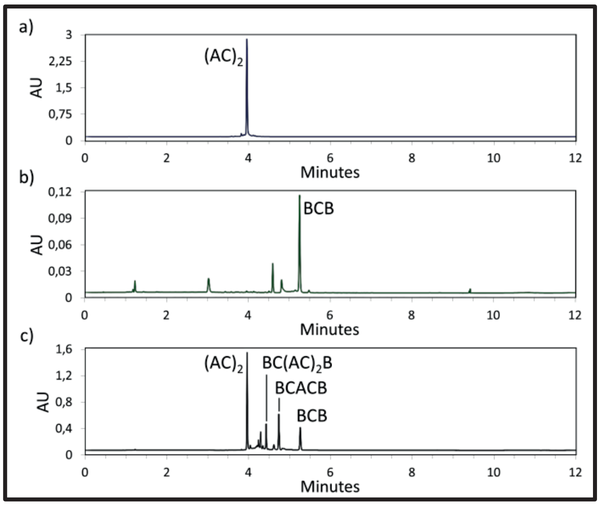


Figure 1. Chromatograms of the starting hydrazone solutions. *a*) DCL prepared from building blocks **A** and **C** (1.0 mM each); *b*) DCL prepared from building blocks **B** (2.0 mM) and **C** (1.0 mM); *c*) DCL prepared from building blocks **A** (0.50 mM), **B** (1.0 mM), and **C** (1.0 mM). All solutions were prepared in aqueous ammonium acetate buffer (50 mM, pH = 4) and were incubated for 12 days prior to UPLC analysis.

For the UV irradiation experiments we prepared solutions (**A**, **C**), (**B**, **C**), and (**A**, **B**, **C**) (ammonium acetate buffer, 50 mM, pH 4; total concentrations of hydrazide and aldehyde groups 2.0 mM; see *Table S2*). After one day of equilibration, we added **A** to (**B**, **C**), **B** to (**A**, **C**), and both hydrazides to (**A**, **B**, **C**), thus obtaining solutions with the same concentrations of **A**, **B**, and **C** units – 0.50 mM, 1.0 mM, and 0.50 mM, respectively – but from three different starting points. Freshly prepared solutions were analyzed by UPLC, and immediately afterwards each solution was split into two parts: one to be exposed to UV irradiation (365 nm) for a day, and the other to equilibrate in the dark over the same period. Monitoring was also performed by UPLC. The results show a strong effect of UV irradiation on the behavior of the libraries. The compositions of the irradiated solutions reached similar and steady levels in less than 20 h (*Figure 2*, *a* and *b*), while the solutions that were not irradiated had still significantly different compositions at that point (*Figure 2*, *c* and *d*). It is interesting to note that the intermediate species exhibited an initial increase of their concentrations, followed by a decrease, particularly visible in the solutions that were equilibrating in the dark (*Figure 2*, *d*). This suggests that **BCACB**, **BC**(**AC**)$_2$**B**, and other intermediate species are not intermediate only in the sense of their compositions, but are also intermediate products of the hydrazone exchange when it starts from the terminal species. Similar kinetic profiles have also been reported in self-sorting DCLs [87 – 90].

To confirm these observations, we performed another experiment with the same basic setup, but with the final concentrations of **A**, **B**, and **C** units of 0.25 mM, 1.0 mM, and 0.25 mM, respectively (*Table S3*). From the decrease in the concentration of hydrazones we expected a corresponding decrease in exchange rates, while the larger excess of **B** was expected to give a larger amount of **B**-containing hydrazones that were present in very small quantities in the initial setup. The results of this experiment (*Figure S28*) indeed showed decreased exchange rates, but the irradiated solutions still reached similar compositions within a day. The relative amounts of the **B**-containing hydrazones, however, remained small, only to confirm the strength of the macrocyclic effect.

We investigated whether the increased exchange rates were indeed the effect of irradiation, and not merely a consequence of the heat released by the UV lamp. In additional control experiments we also investigated how much the photodynamic states differ from the equilibrium states. When

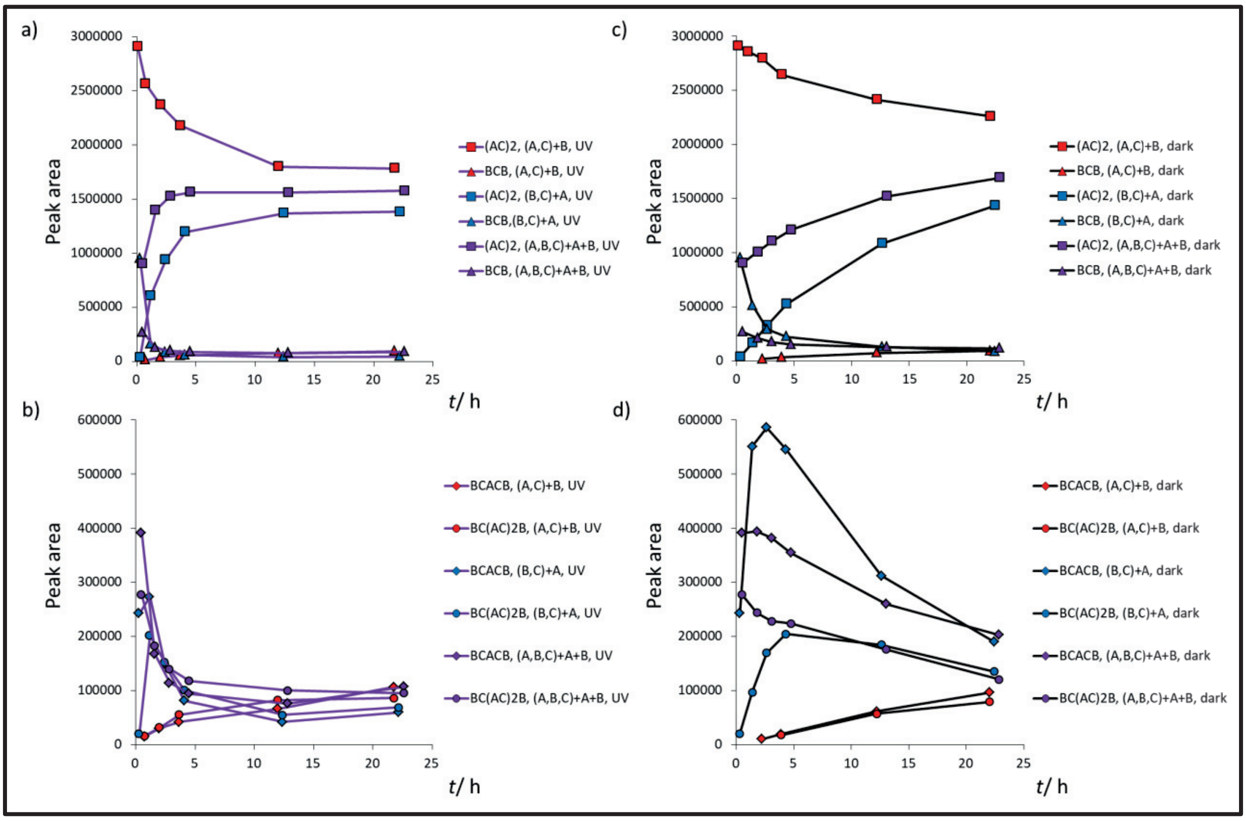


Figure 2. **Changes in composition of irradiated** (*a* and *b*) **and non-irradiated** (*c* and d) **non-equilibrated hydrazone libraries**. Three different non-equilibrated libraries ((**A**, **C**)+**B**, containing **A** (0.50 mM) and **C** (0.50 mM) coupled into hydrazones, and free **B** (1.00 mM); (**B, C**)+**A**, containing **B** (1.00 mM) and C (0.50 mM) coupled into hydrazones, and free **A** (0.50 mM); and (**A, B, C**)+**A**+**B**, containing **A** (0.25 mM), **B** (0.50 mM) and **C** (0.50 mM) coupled into hydrazones, and free **A** (0.25 mM) and **B** (0.50 mM)) were each split into parts exposed to UV irradiation (*a* and *b*), or left to equilibrate in the dark (***c*** and *d*). Both terminal (*a*) and intermediate (*b*) species in the irradiated libraries reach similar and stable concentrations in less than 20 h, while in the non-irradiated libraries (***c*** and *d*) equilibrium is not reached in the same period. All solutions were prepared in aqueous ammonium acetate buffer (50 mM, pH 4).

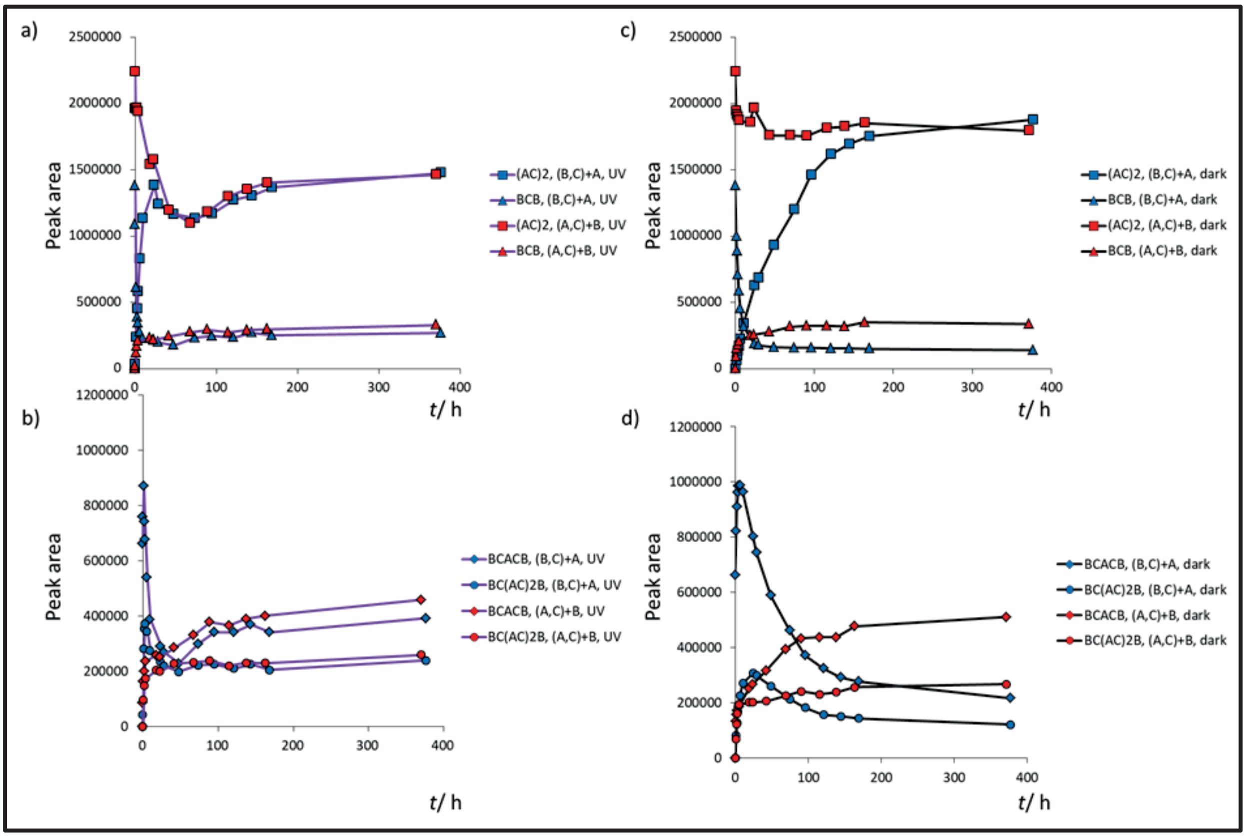


Figure 3. UV-accelerated hydrazone equilibration. Two different non-equilibrated libraries ((**A**, **C**)+**B**, containing **A** (0.50 mM) and **C** (0.50 mM), coupled into hydrazones and free **B** (1.00 mM); and (**B**, **C**)+**A**, containing **B** (1.00 mM) and **C** (0.50 mM) coupled into hydrazones and free **A** (0.50 mM)) were each split into parts exposed to UV irradiation (UV), or left to equilibrate in the dark, away from the UV lamp (*dark*). In the irradiated samples (*a* and *b*) photoequilibrium was reached after 2 days of irradiation. Irradiation was then discontinued, and all samples were left to equilibrate in the dark. After 5 days, the samples that were initially irradiated reached stable concentrations. The non-irradiated samples (*c* and *d*) took about two weeks to equilibrate. All solutions were prepared in aqueous ammonium acetate buffer (50 mM, pH 4).

only small differences between the equilibrium and photodynamic states would be observed, this would imply that UV irradiation can be used to accelerate hydrazone equilibration.

The first question was addressed by measuring the temperature of samples during irradiation. This was done using a small temperature probe and blank samples containing water, which were either exposed to the irradiation from the UV lamp, or placed away from the lamp. The measurements showed that the UV lamp indeed heated the samples. However, the temperature of the irradiated sample stabilized after 3 h of irradiation to 2–3 °C above room temperature (*Figure S31*). The temperature measurements thus show that the effect of heating is small, which means that the observed behavior of the irradiated libraries cannot be attributed to the increase of temperature, but predominantly to the UV irradiation (*Figure 3, top*)

The second question essentially requires that the samples kept in the dark reach equilibrium, as only then it can be assessed whether irradiation indeed shortens the time needed to reach equilibrium, or it leads to other outcomes, such as kinetic trapping or photodegradation. We again prepared solutions (**A**, **C**) and (**B**, **C**) (setup in *Table S4*), and, after a day of equilibration, added **B** to (**A**, **C**) and **A** to (**B**, **C**), thus obtaining solutions (**A**, **C**)+**B** and (**B**, **C**)+**A**, each with final concentrations of **A**, **B**, and **C** units of 0.50 mM, 1.0 mM, and 0.50 mM, respectively, but with different starting points with respect to hydrazones and free hydrazides. After the initial UPLC analysis, performed immediately after preparing the samples, each solution was split into two parts. As in the previous experiments, they were either exposed to UV irradiation (UV), or kept in dark (*dark*). After 2 days of irradiation, the UV lamp was switched off, and all samples were monitored while kept in dark until the non-irradiated samples reached the equilibrium state.

As previously observed, the concentrations of the library constituents in the irradiated libraries reached similar levels after about one day, while the non-irradiated libraries were still far from the equilibrium state at that moment (*Figure S29*). After another day of irradiation, the concentrations of the monitored species reached constant values, indicating that the library had reached a dynamic stationary state. Irradiation was then stopped, causing the concentrations of the library constituents to undergo modest changes. After 5 days of standing in the dark, the concentrations stabilized at values that were not far from those in the photostationary state (*Figure 3*, *a* and *b*). Altogether, in about a week after the start of the experiment, the irradiated libraries have reached the equilibrium state. In the non-irradiated libraries, on the other hand, some library members reach what appears to be their equilibrium state in about two weeks (*Figure 3*, *c*), while others have still not reached a constant concentration (*Figure 3*, *d*).

In the final states of the libraries (*Figure 3*) the amount of the $(\mathbf{AC})_2$ tetramer is somewhat lower in the irradiated samples compared to the non-irradiated ones. This difference is most likely caused by (largely non-selective) photodegradation of the hydrazones.

The results above show that it is possible to significantly shorten the time needed for exchange in acyl hydrazone libraries using UV light, in this example from about two weeks to one day (for the photostationary state) or one week (for subsequent equilibration). The disadvantage of this approach is, however, a small extent of photodegradation, as exemplified by the decreased amounts of the $(\mathbf{AC})_2$ tetramer in the irradiated libraries. Thus, in designing experiments where UV light will be used to accelerate hydrazone exchange some effort should be put into finding the balance between the time saved by shortening the duration of the experiments, and the library material loss due to the photodegradation. These results also demonstrate that photomediated hydrazone exchange occurs faster than the corresponding thermal exchange, indicating that photoirradiation may provide access to out-of-equilibrium library distributions. While in the present system the equilibrium distribution and the photodynamic state were similar, in systems where different library members interact with light with different efficiencies, the thermal and photodynamic states should be substantially different.

Conclusions

In this research we have shown that responsiveness of (acyl) hydrazone libraries to UV irradiation, and the consequent formation of photodynamic DCLs, aside from their use in design of responsive or adaptive systems, can be used to address a long-standing problem in hydrazone chemistry. Namely, as UV irradiation can quickly transform any hydrazone-based DCL into a photodynamic DCL, formation of such systems by irradiation can serve to reduce the time required for performing hydrazone exchange. This can be particularly useful for systems where thermal (*E*)/(*Z*) isomerization is fast, and may find use wherever equilibration is unacceptably slow.

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Authors' contributions

All authors have given approval to the final version of the manuscript.

Competing interests

The authors declare that they have no competing interests.

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Additional files

Supporting Information: Materials, analytical methods, preparation and characterization of hydrazones, preparations of libraries, LC-MS data, additional experiments.