Probing the limits of selectivity in a recognition-mediated reaction network embedded within a dynamic covalent library

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Abstract: Two recognition-mediated reaction processes operating through a reactive binary complex drive resolution of a 24-component dynamic covalent library, assembled from individual aldehydes and nucleophiles. The effectiveness of the library resolution and selective amplification of one recognition-enabled species over another is limited by the difference in the rates of the recognition-mediated reactive processes and strength of the recognition processes employed in the dynamic system.

Introduction

Complexity in the world around us does not simply develop as a function of the increasing number of components within a given system. Instead, it emerges within systems that possess the ability to dynamically self-organise and in which feedback between components is present. The capacity of individual components within a system to interact allows these individual elements, with established properties, to come together and form constructs of higher order, giving rise to emergent behavior and properties. Simultaneously, the interconnectedness of all components enables complex systems to constantly adapt and evolve in response to environmental stimuli. Our inability to control and predict the behaviour of complex systems is an essential feature that allows us to differentiate them from systems that are merely complicated, such as machines or engines, where components interact in a controlled and predictable manner. Only by exploring the role of connectivity and the fundamental relationship between the components of interconnected networks can we begin to develop an understanding of how complex systems may have played a role in the transition from simple compounds to the first self-sustaining system.

The study of a complex chemical network begins with its design. One method that has been shown to be particularly effective in generating complex interconectec systems is dynamic covalent chemistry (DCC). The general combinatorial approach and reversible bond formation allow facile construction of dynamic covalent libraries (DCLs) of interconverting components under thermodynamic control. When a DCL is instructed by the addition of an external stimulus, the equilibrium distribution is altered and the library components stabilised by the interaction with the stimulus are amplified. However, the purely thermodynamic selection limits the magnitude of amplification that can be achieved within the DCL. In order to attain increased selectivity within DCLs, we have to employ methods that couple DCLs to irreversible processes and allow the target to be removed from a pool of exchanging components through kinetic selection. In the past, several successful examples, demonstrating target amplification using both chemical reactions and physical processes, have been reported. Recently, we have reported the use of a single, recognition-mediated irreversible 1,3-dipolar cycloaddition reaction as the means of selecting and amplifying a specific target from within a dynamic library composed of interconverting nitrones and imines. Specifically, we explored two different kinetic modes for achieving DCL resolution (Figure 1), driven by (i) formation of a reactive binary complex (AB, Figure 1) or (ii) template-mediated self-replication (SR, Figure 1). In this work, we examine the factors that govern the selectivity in a DCL, assembled from individual aldehydes and nucleophiles, incorporating a reaction network involving not one, but two recognition-mediated processes operating through a reactive binary complex. With specific focus on this mode of selection within the DCL, we demonstrate how changing the strength of recognition processes within the system influences the effectiveness of resolution within the library.

Results and Discussion

Our dynamic covalent library (Figure 2) is based on a 4 x 4 matrix of aldehydes, A to D, and nucleophiles, W to Z, comprised of three amines and one hydroxylamine, which afford an exchange pool of 12 imines and 4 nitrones. The total of 24 interconverting components represents a dynamic system that can be analysed readily by 19F NMR spectroscopy – the presence of either an ary1-F or trifluoromethyl (-CF3) tag on each nucleophilic component facilitating the identification of individual components in the library.

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Supporting information for this article is given via a link at the end of the document.
Figure 2. Dynamic covalent library composed of four aldehydes, A to D and four nucleophiles, W to Z. Corresponding exchange pool components and cycloadducts, formed upon reaction with recognition-enabled maleimide M and recognition-disabled M_dis, containing aldehyde A are in black, aldehyde B are in grey, aldehyde C and aldehyde D are white.

The library is designed to contain components equipped with two distinct features: a reactive site and a recognition element. Formation of a reactive nitrone is provided by reaction of aldehydes with hydroxylamine Z. The library also contains two aldehydes bearing a site capable of recognising a carboxylic acid: A (4,6-dimethyl amidopyridine) and B (6-methyl amidopyridine). Overall, the library exchange pool contains only two components, AZ and BZ, equipped with both a reactive and a
of nitrones from hydroxylamine Z lies far towards the product side, with almost complete conversion (>99%) to the corresponding nitrones. The two recognition-enabled nitrones, AZ and BZ, are present at a higher concentration than non-recognition nitrones CZ and DZ. Interestingly, the more electron rich pyridine ring present in aldehyde A makes it less reactive towards nucleophiles than aldehyde B, resulting in a slightly higher concentration of BZ (6.72 mM) than AZ (6.39 mM).

**The Exchange Pool**

Initially, we needed to confirm that our library forms a dynamic exchange pool. Determination of the equilibrium distribution of our DCL in the absence of any recognition-mediated reactions will enable us to quantify the magnitude of perturbation of the DCL composition upon addition of instructing maleimide. In a typical experiment, an equimolar solution of aldehydes and nucleophiles ([A] to [D] and [W] to [Z] = 20 mM) was prepared in CD$_2$Cl$_2$ saturated with para-toluenesulfonic acid monohydrate (PTSA). The solution was incubated at 273 K and the product distribution was determined by quantitative $^{19}$F($^1$H) NMR spectroscopy (282.4 MHz) after 5 days (for details, see Supporting Information). However, as a result of insensitivity of the -CF$_3$ group to changes in its surrounding electronic environment, we were unable to resolve individual resonances for the Y-imines bearing the trifluoromethyl tag. The distribution of condensation products in the library exchange pool is presented in Figure 4. The equilibrium position for the formation of nitrones from hydroxylamine Z lies far towards the product side, with almost complete conversion (>99%) to the corresponding nitrones. The two recognition-enabled nitrones, AZ and BZ, are present at a higher concentration than non-recognition nitrones CZ and DZ. Interestingly, the more electron rich pyridine ring present in aldehyde A makes it less reactive towards nucleophiles than aldehyde B, resulting in a slightly higher concentration of BZ (6.72 mM) than AZ (6.39 mM).

**Kinetic Selection in the Absence of the DCL**

Prior to instructing the DCL through addition of maleimide M, we needed to rule out inherently different reactivities of the two nitrones towards maleimides as a potential factor contributing to the selectivity for the formation of any one cycloadduct. In this respect, we constructed a series of kinetic experiments (Figure 5) that would establish the reactivity of both AZ and BZ nitrones in the absence of any dynamic components. Firstly, the

**Figure 3.** cis Selective 1,3-dipolar cycloaddition between nitrones AZ and BZ with maleimide M proceeds via the recognition-mediated formation of [AZ-M] and [BZ-M] reactive binary complexes.

**Figure 4.** (a) Distribution of the DCL exchange pool after five days at 273 K, as determined by (b) $^{19}$F($^1$H) NMR spectroscopy (282.4 MHz), relative to 1-fluoro-4-nitrobenzene as the internal standard ([A] to [D] and [W] to [Z] = 20 mM in CD$_2$Cl$_2$ saturated with para-toluenesulfonic acid monohydrate). The resonances for Y-imines could not be resolved as a result of the insensitivity of the -CF$_3$ tag to changes in its electronic environment.
individual reactions of each nitrone with a recognition-disabled maleimide \(M_{\text{ds}}\) were examined. The carboxylic acid on \(M_{\text{ds}}\) is protected as the methyl ester, rendering it incapable of recognition-mediated interactions and by examining its reaction with the two recognition nitrones, we can establish the rate constants and diastereoselectivity associated with the bimolecular pathways.

![Flow chart outlining a series of experiments designed to probe the origins of selectivity in a recognition-mediated network embedded in a dynamic covalent library.](image)

**Figure 5.** Flow chart outlining a series of experiments designed to probe the origins of selectivity in a recognition-mediated network embedded in a dynamic covalent library. Both the DCL and the irreversible reactions have to be examined in isolation and in a competition scenario in the presence of recognition-disabled maleimide \(M_{\text{ds}}\) and recognition-enabled maleimide \(M\) (grey box).

Secondly, analysis of the reaction of \(AZ\) and \(BZ\) with a recognition-enabled maleimide \(M\) allows us to determine the rate and selectivity enhancement gained through recognition in a purely kinetic scenario. Thirdly, probing the reactivity of both nitrones under competition conditions, in the presence of either recognition-disabled maleimide \(M_{\text{ds}}\) or recognition-enabled maleimide \(M\) provides us with a direct measurement of selectivity afforded through kinetic selection only. These three isolated kinetic experiments will, ultimately, allow us to evaluate the extent of contribution of dynamic selection to the overall selectivity in the recognition-network. We employed three experiments in order to probe the selectivity within a DCL. Analysis of the exchange pool distribution in the absence of any maleimide was described in Figure 4. Two additional DCL experiments were designed to complement the competition kinetics performed with \(M_{\text{ds}}\) and \(M\) maleimides in the absence of DCL, and are presented in a later section.

In each kinetic experiment, a sample containing the nitrone(s) and the maleimide at 20 mM was prepared in CDCl\(_3\), and are presented in Figure 4. Analysis of an interconnected recognition-mediated network embedded in a dynamic covalent library allows us to determine the rate and selectivity enhancement gained through recognition.

**Table 1.** Kinetic and association constants determined for the reaction of \(AZ\) and \(BZ\) with \(M\) and \(M_{\text{ds}}\) by kinetic simulation and fitting of experimental data using the SimFit program.

<table>
<thead>
<tr>
<th>(\text{Bimolecular rate constant} / \text{s}^{-1})</th>
<th>(\text{Kinetic rate constant} / \text{s}^{-1})</th>
<th>(\text{Effective molarity} / \text{M}^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1.24 \times 10^{-5})</td>
<td>(1.24 \times 10^{-5})</td>
<td>(5.37 \times 10^{-6})</td>
</tr>
<tr>
<td>(1.30 \times 10^{-4})</td>
<td>(1.30 \times 10^{-4})</td>
<td>(5.93 \times 10^{-5})</td>
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Employing the fitting procedure (see Supporting Information), kinetic experiments with recognition-disabled maleimide \(M_{\text{ds}}\) confirmed that, in the absence of recognition, the cycloaddition reactions are slow and unselective, resulting in less than 20% conversion to cycloadducts after 15 hours, with cis/trans diastereoisomeric ratio of \(-12.3\) in each experiment. The outcome of analogous reactions with maleimide \(M\) clearly demonstrated the effect of enabling molecular recognition, revealing conversion to cycloadducts of \(>85\)% after 15 hours and more than 40:1 selectivity for the cis diastereoisomer. Concentration-time data for the four isolated kinetic experiments were fitted to the appropriate kinetic model (see Supporting Information), constructed to encompass all the interactions in each system as well as the estimated association constants, thus allowing us to extract kinetic parameters for the individual reactions of \(M\) and \(M_{\text{ds}}\) with nitrones \(AZ\) or \(BZ\) (Table 1).

| Association constant \(K_{\text{a}} / \text{M}^{-1}\) | 315 | 150 |
Fitting of the concentration vs time data revealed that the enhancement in the recognition mediated-reaction relative to bimolecular rate constant (effective molarity, EM) is largely similar for both reactions, with an EM ratio of 1.1:1 for AZ:BZ. Therefore, the uneven population of cis-AZ and cis-BZ is predominantly influenced by the different affinities of AZ and BZ for M, with smaller contribution exerted also by the individual variations in reactivity. We envisaged that competition for a shared building block might present a different outcome when the reaction network is embedded in a dynamic library. More specifically, we hoped that the absence of preformed nitrones would allow the added maleimide to selectively pull material from the exchange pool and form the product with a higher association constant preferentially, amplifying the difference between the two cis products in the processes.

**Recognition-mediated Resolution**

In order to ascertain that simply performing the cycloaddition reaction in the presence of a DCL does not generate any significant changes in composition, the DCL was first addressed with a recognition-disabled maleimide M_disabled. Under recognition-disabled conditions, all four nitrones can only react through a slow, bimolecular reaction. A library sample ([A] to [D] and [W] to [Z] to [Z] = [M_disabled] = 20 mM, CDCl₃ saturated with para-toluenesulfonic acid monohydrate) was analysed by ²⁹F¹H NMR spectroscopy (282.4 MHz) after 5 days at 273 K (Figure 7a). The exchange pool distribution remained largely unaffected by the slow and unselective cycloaddition reactions, with only 40% overall conversion to all 8 cycloadducts. The four nitrones exhibited similar reactivities, and it was clear that simply incorporating an irreversible reaction into a DCL did not afford selectivity for the recognition species.

We next examined the effect of recognition-enabled maleimide M on the library distribution and product selectivity. An equimolar solution containing all reaction components ([A] to [D] and [W] to [Z] = [M] = 20 mM) was prepared in CDCl₃ saturated with PTSA and the solution examined by ²⁹F¹H NMR spectroscopy (282.4 MHz) after 5 days at 273 K. Addition of the recognition-enabled maleimide M had a profound effect on the distribution of the product pool (Figure 7b). Recognition-enabled cycloadducts cis-AZ and cis-BZ were present in a ratio of 1.1:1,
at a significantly higher concentration than any other product, with 45% and 41% conversion respectively.

The higher $K_a$ value for the recognition processes in cis-AZ manifested itself in the marginally higher proportion of this product than that of cis-BZ. The effect of introducing recognition was also immediately noticeable within the exchange pool. The library components equipped with the recognition site are significantly depleted in response to the decreasing amounts of AZ and BZ nitrones. The release of the W and X exchange pool components from their A- and B-imines results in increased concentrations of the C- and D-imines, incorporating these components. Figure 7c shows the magnitude of the recognition effect on the DCL distribution, highlighting the difference between the concentrations of exchange pool in the recognition-enabled scenario relative to exchange in the absence of any maleimide. The increased concentration of non-recognition imines illustrates how the connectivity of a network can allow system-wide effects to emerge.

Origins of Limited Selectivity
Selectivity in a system with two simultaneous and irreversible kinetically-driven processes is inherently limited by the reaction conditions and the kinetic parameters governing these processes. The isolated kinetic experiment, where AZ and BZ nitrones competed for a limited amount of recognition maleimide M, revealed that the more strongly binding amidopyridine unit allows AZ to associate and react to a greater extent than BZ nitrone. The final ratio in this experiment was 1.2:1 in favour of cis-AZ. We hoped that the ratio would be amplified upon transferring the competing recognition-mediated reaction network to a dynamic environment. However, embedding the network within a DCL showed a negligible effect on the formation of these two products and selectivity remained essentially unchanged (Figure 8).

Figure 8. Concentration of cis-AZ (black) and cis-BZ (grey) formed under kinetic conditions after 15 hours and within the environment of DCL after five days (cis-AZ:cis-BZ = 1:2:1) and within the environment of DCL after five days (cis-AZ:cis-BZ = 1:1:1). The area of the circle denoted by the dotted line represents 100% conversion of maleimide M, whereas the relative areas of the pie charts are scaled to represent the actual conversion to recognition-enabled products under kinetic selection (96%) and kinetic and dynamic selection (85%).

While the dynamic selection did not provide the desired increase in selectivity, the recognition events exerted a dramatic effect on the product distribution (Figure 7b vs Figure 7a) in the library and facilitated selection of species equipped with recognition elements effectively. AZ, BZ, A, B and Z exchange pool components were removed selectively from the mixture of interconnected components despite the fact that they were present as minor components. Employing dynamic conditions together with recognition-mediated irreversible reaction revealed that the small difference in the strength of association constants cannot be amplified beyond the limit imposed by kinetic selection.

In order to probe the origins of the limited selectivity in our dynamic recognition-mediated network, we constructed a kinetic model incorporating all of the reactions leading to the formation of exchange pool products (for details, see Supporting Information). Rather than individually measuring rate constants for each reaction, we decided to identify trends in the reactivity of each component from the distribution of the exchange pool in isolation. Simulation of the exchange pool in the absence of any maleimide (for details, see Supporting Information) showed a good agreement with the experimental data (Figure 4) presented already. Utilising our simulation, we were able to vary the rates of exchange reactions with respect to the rate of cycloaddition, setting them to be much higher, very similar or significantly lower than the rate of cycloaddition reaction. Comparison of the simulated DCL distribution to the experimentally determined results revealed that our system behaves akin to a fast exchange simulation (for details, see Supporting Information). The rates of exchange reactions have a specific effect on the selectivity for recognition products, as well as on the ratio of cis-AZ/cis-BZ within the library. Any imbalance in the concentrations of AZ and BZ generated through the irreversible reactions is erased by exchange with other library members containing the recognition and reactive materials (A, B and Z), thus allowing the recognition-mediated reaction to proceed efficiently. In our library, the starting components are present at 20 mM, a concentration considerably above the $K_d$ for both competing association processes. The fast exchange reactions allow a significant concentration of both nitrones to build up, enabling both recognition processes to operate efficiently. In this respect, the dynamic scenario becomes similar to a simple kinetic experiment. We envisaged that operating the system at concentrations closer to or below the $K_d$ for the formation of both binary complexes, [AZ·M] and [BZ·M], would enable the initial imbalance towards one recognition product to be propagated. In this respect, we set out to investigate what conditions promote selectivity in a reaction network embedded in a DCL and whether the same conditions have a comparable influence on the network under simple kinetic selection. In order to do so, we examined the effect of varying three variables: (i) initial concentration, (ii) ratio of association constants for the formation of [AZ·M] and [BZ·M] and (iii) ratio of effective molarities for reactions of AZ and BZ nitrones. These three variables were examined under four different simulation conditions, I to IV (Figure 9).
Conversion to cycloadducts after a specific time (5 days) in a concentration to elucidate the effect of varying kinetic parameters at different the higher ratio of EM (experimental corresponding to the fitted parameters determined for our system. Four sets of conditions with AZ/BZ processes at different K values and EM ratios were examined: Condition I employed the K and EM ratio corresponding to the fitted parameters determined for our experimental system, Conditions II to IV simulated either a higher ratio of EM (II), K (III) or both EM and K values (IV).

Simulations were performed using the SimFit software package (Günter von Kiedrowski, University of Bochum, 2008). In each condition, grey rectangles represent the concentration range that affords the best selectivity for overall formation of cycloadducts and the highest percentage of recognition-enabled species in the cycloadduct pool (N.B.: In all cases, the x-axis is represented in logarithmic scale).

Each simulation examined a different ratio of K values and EM ratios at 10 different initial concentrations, ranging from 0.05 to 200 mM. We focused on examining the effect of changing initial conditions and reaction parameters on the ratio of cis-AZ/cis-BZ formed, the overall conversion to cycloadducts and percentage of recognition-enabled products (cis-AZ and cis-BZ) present in the product pool. Condition I employed the K and EM ratio corresponding to the fitted parameters determined for our experimental system. Conditions II to IV simulated either a higher ratio of EM (II), K (III) or both EM and K values (IV) for the AZ/BZ recognition processes. These simulations allowed us to elucidate the effect of varying kinetic parameters at different concentrations on the ratio of cis-AZ/cis-BZ (Figure 9a) and conversion to cycloadducts after a specific time (5 days) in a kinetic scenario (Figure 9b) and in the environment of a DCL (Figure 9c).

Condition I enabled us to determine what influence different initial concentration would have on our experimental system. At 20 mM initial concentration (Condition I), we found the simulated ratio of cis-AZ/cis-BZ within a DCL to be very similar to the experimentally determined values for dynamic selection, confirming it to be an accurate model of our dynamic library system. The simulated ratio of cis-AZ/cis-BZ is lower in the DCL selection than in the kinetic selection, and continues to fall with decreasing concentration of starting materials (for details, see Supporting Information). This observation, while counterintuitive, can be attributed to the recognition nitrone AZ being present at lower concentrations than the nitrone BZ in the library. As mentioned previously, the higher electron density around the pyridine ring in BZ nitrone makes the aldehyde component B less reactive towards hydroxylamine Z. This effect becomes more pronounced at lower initial concentrations (for details, see Supporting Information), effectively eroding the advantage.

Figure 9. Outcome of simulations examining the effect of initial concentration on (a) ratio of cis-AZ/cis-BZ, (b) and (c) conversion to all cycloadducts and percentage of the recognition-enabled products in the product pool, in reaction network under kinetic selection and within a dynamic environment after 5 days, respectively. Four sets of conditions with AZ/BZ processes at different K values and EM ratios were examined: Condition I employed the K and EM ratio corresponding to the fitted parameters determined for our experimental system, Conditions II to IV simulated either a higher ratio of EM (II), K (III) or both EM and K values (IV). Simulations were performed using the SimFit software package (Günter von Kiedrowski, University of Bochum, 2008). In each condition, grey rectangles represent the concentration range that affords the best selectivity for overall formation of cycloadducts and the highest percentage of recognition-enabled species in the cycloadduct pool (N.B.: In all cases, the x-axis is represented in logarithmic scale).
available to AZ nitrone as a result of its higher $K_a$ value. A similar effect on the cis-AZ/cis-BZ ratio was not observed in conditions II to IV, likely because the increasing $K_a$ and EM ratios compensate for the lower reactivity. Increasing either the $K_a$ or EM ratio (Condition II and III) revealed that it is possible for a lower concentration to have the desired effect on the selectivity within a system, if the $K_a$ or EM ratios for the two competing processes are larger than those expressed by AZ and BZ in our experimental system. In fact, analysis of Condition IV revealed that a concurrent increase in both $K_a$ and EM ratio affords an even more significant increase in selectivity for one recognition cycloadduct in the system. Nevertheless, as observed experimentally for nitrone AZ, we know from experience that increasing the strength of recognition on element A can potentially also affect the reactivity of this component towards nucleophiles and its ability to exchange within the library. However, as we have no means of predicting the extent to which the aldehyde reactivity might be affected, we cannot account for it in the simulation and the rates of exchange reactions are kept constant throughout the simulations. We further examined the influence of simulated initial conditions on the overall conversion to cycloadducts and the percentage of recognition-enabled species in the product pool. The simulations showed that there is an optimum window of concentration for obtaining the best selectivity for recognition products within each set of conditions. Furthermore, we found that selectivity for products formed through recognition-mediated reactions is affected more strongly by decreasing concentration within a DCL as compared to under kinetic selection. A drop in selectivity for recognition species is also observed at higher concentrations as a result of increased contribution of the bimolecular pathway to the overall product pool. However, this effect is more noticeable in conditions employing the rather low experimental EM ratio.

These kinetic simulations demonstrate that a clear set of rules exists that describes library performance. A substantial increase in selectivity for cis-AZ over cis-BZ can only be achieved under Condition IV. In this situation, both the ratio of association constants and the ratio of effective molarities for the two recognition-mediated processes within the reaction network embedded are 10. In these circumstances, better selectivity is achieved when the selection occurs from the DCL. However, the optimum concentration ranges for selectivity (grey zones, Figure 9) are significantly narrower when selection occurs from the DCL as opposed to purely kinetically. The narrowing of the optimum concentration window is proportional to the number of compounds present within the DCL – the larger the library, the narrower the window will be.

Ultimately, while the simulations here allow us to determine the effect of different recognition and reaction parameters on the selectivity generated in this system by two reactive binary complexes within a DCL, non-linear reaction processes, such as autocatalysis, are an obvious extension and implementing these processes within DCLs may, in principle, generate more dramatic selectivity for a single product, this expectation awaits experimental testing.

Conclusions

A simple recognition event has a profound effect on the distribution of a dynamic library and can be used to amplify chemical species from within a number of interconverting components. Nevertheless, the rapid exchange reactions within the dynamic library and the experimental conditions employed enable both recognition-mediated reaction processes to operate efficiently, thereby allowing kinetic selection to prevail. Through simulations and kinetic fitting, we were able to develop an understanding of the intricate interconnected network and formulate a set of rules that govern the selectivity within the dynamic system and how it compares to selectivity in a purely kinetic scenario. Finally, we have demonstrated that working at concentrations below the $K_a$ values of the recognition processes can positively influence the difference in selectivity between two amplified species. However, in order to induce significant selectivity in a recognition-mediated system, the difference in the association constants and the effective molarities of the employed recognition and reactive elements must be much greater than in our current experimental system. The results presented here suggest that the successful resolution of DCLs, where multiple recognition-mediated pathways are open to the system, may be impractical. Therefore, resolution of DCLs using irreversible recognition-mediated approaches may have to rely on the interplay of multiple kinetic selection modes, e.g. binary reactive complexes and autocatalytic templates, in order to be effective. This strategy is currently under investigation in our laboratory.

Acknowledgements

This work was supported by the award of a Postgraduate Studentship from EPSRC (EP/K503162/1) to TK. The research data supporting this publication can be accessed at http://dx.doi.org/10.17630/2a427a7e-d025-492e-9301-377e18459060.
Keywords: molecular recognition • combinatorial chemistry •
cycloaddition reaction • NMR spectroscopy • kinetics

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