Teaching an Old Compound New Tricks: Reversible Transamidation in Maleamic Acids

Bartosz M. Matysiak[+],[a] Guillermo Monreal Santiago[+],[a] and Sijbren Otto*[a]

Abstract: Dynamic combinatorial chemistry is a method widely used for generating responsive libraries of compounds, with applications ranging from chemical biology to materials science. It relies on dynamic covalent bonds that are able to form in a reversible manner in mild conditions, and therefore requires the discovery of new types of these bonds in order to progress. Amides, due to their high stability, have been scarcely used in this field and typically require an external catalyst or harsh conditions for exchange. Compounds able to undergo uncatalysed transamidation at room temperature are still rare exceptions. In this work, we describe reversible amide formation and transamidation in a class of compounds known as maleamic acids. Due to the presence of a carboxylic acid in β-position, these compounds are in equilibrium with their anhydride and amine precursors in organic solvents at room temperature. First, we show that this equilibrium is responsive to external stimuli: by alternating the additions of a Brønsted acid and a base, we can switch between amide and anhydride several times without side-reactions. Next, we prove that this equilibrium provides a pathway for reversible transamidation without any added catalyst, leading to thermodynamic distributions of amides at room temperature. Lastly, we use different preparation conditions and concentrations of Brønsted acid to access different library distributions, easily controlling the transition between kinetic and thermodynamic regimes. Our results show that maleamic acids can undergo transamidation in mild conditions in a reversible and tunable way, establishing them as a new addition to the toolbox of dynamic combinatorial chemistry.

Introduction

Dynamic combinatorial chemistry (DCC)[1,2] emerged two decades ago as a tool to develop complex networks of chemical reactions from relatively simple building blocks. The approach of DCC is based on covalent bonds that undergo exchange under relatively mild conditions, leading to a library of products in thermodynamic equilibrium. Due to their ease of preparation and responsiveness to external triggers, dynamic combinatorial libraries (DCLs) based on this approach have found applications in a variety of fields, such as responsive systems and materials,[2–6] design of enzyme inhibitors,[7–11] cell recognition,[12] and self-replicating molecules.[13,14] These applications are restricted to the dynamic bonds that are available,[15–22] each of them with limitations in terms of experimental conditions and functional group compatibility. As the applications of DCC

grow, there is also an increasing demand for the discovery of new dynamic bonds to expand its scope.[23]

Amide bonds, in principle, seem to be the opposite of dynamic. Due to their high kinetic stability, amide hydrolysis or transamidation reactions typically require either harsh conditions ($> 250\,°C$), stochiometric reagents[24,25] or long reaction times. DCLs of amides have, however, been reported in a few occasions. Stahl[26] described amide exchange at room temperature using organic solvents and transition metal catalysts. Ulijn[27,28] used enzymatic catalysis to prepare peptide DCLs from which self-assembled structures emerged, while Flitsch[29] used proteases for the transamidation of peptides attached to gold surfaces. Finally, the groups of Giuseppone[30] and Melnyk[31] used peptides containing cysteine or selenocysteine to undergo amide transfer mediated by N→S(Se) transacylation in a process that they named "reversible native chemical ligation". In these last two cases, the exchange reaction needed to be activated - either by covalent modification of the starting amide, in the case of peptides containing cysteine, or by addition of an organocatalyst to activate the transient selenoester, for seleno-cysteine-containing peptides.

In this work, we describe a new class of DCLs based on the reversible formation of amide bonds without any catalysts and in mild conditions. The amides chosen for this purpose are N-substituted maleamic acids, a class of vinyl amides that contain a carboxylic acid in β-position. These amides are known since the 1950s for their high rates of hydrolysis.[32,33] This hydrolysis is mediated by the intramolecular formation of a cyclical anhydride from the carboxylic acid and amide groups, and requires the acid to be protonated.[34–37] Therefore, they have been

[a] B. M. Matysiak,[+] G. Monreal Santiago,[+] S. Otto
Centre for Systems Chemistry, Stratingh Institute
University of Groningen
Nijenborgh 4, 9747AG, Groningen (Netherlands)
E-mail: s.otto@rug.nl

[+] Equal contribution.

Chemistry–A European Journal

Research Article
doi.org/10.1002/chem.202201043

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commonly used as acid-sensitive protecting groups,[38,39] and as delivery systems.[40–42]

We envisaged that the same mechanism that activates these amides for hydrolysis could be exploited for the formation of DCLs. As described above, maleamic acids tend to react to form the corresponding amine and anhydride. In absence of water or other protic solvent, the anhydride should be stable, leading to an equilibrium distribution that could respond to different changes in conditions. Furthermore, the anhydride could react with other nucleophiles, such as a second amine, reaching an equilibrium distribution between the two resulting amides.

Results and Discussion

As a first step, we studied the formation equilibria of our target compounds. For this, we prepared different N-substituted dimethyl maleamic acids by mixing dimethylmaleic anhydride with amines **1–6** in deuterated acetonitrile. We decided to limit our scope to secondary amines in order to avoid the formation of the undesired N-substituted maleimides, which are normally favoured for primary amines in non-aqueous solutions. Since our study was designed to be a proof of the concept, we chose only symmetrical amines, facilitating the analysis of product mixtures by NMR. An excess of amine (2 equivalents) was added in every case, in order to neutralise the carboxylic acid that forms during the reaction. Dimethylmaleic anhydride was initally selected as a model substrate for its known high reactivity towards hydrolysis,[37] which we expected would be correlated with a higher reactivity towards exchange. In these conditions, we observed the formation of maleamic acids for unhindered aliphatic and benzylic amines (Figures S1–S6) and essentially no reaction for either diphenyl- and diisopropyl-amines (Figures S7 and S8). For the maleamic acids that were formed, there was a remarkable difference in reactivity between aliphatic and benzylic amines, ranging from almost complete conversion in the former (Figures S1, S2, S5 and S6) to almost 40% of unconverted anhydride in the latter (Figures S3 and S4), in the same conditions. This trend was roughly correlated to their pK_bs (aliphatic amines have pK_bs of ~ 3,[43] while benzylic amines have pK_bs of ~ 5[44]). This seems to suggest that the extent to which maleamic acids form is inversely correlated to the leaving group ability of the amine used, morpholine ($pK_b = 5.5$[43]) being an exception in this trend. In order to confirm that the maleamic acids were in equilibrium with their respective precursors, we performed a series of dilution experiments (Figures 1a and S9–S17). As expected, upon diluting the mixtures, the equilibrium was shifted towards the destruction of the maleamic acid and the formation of its amine and anhydride precursors in all cases (Figures S9–S11). In addition to the change in equilibrium concentrations, we observed that diluting the samples also affected the chemical shifts of maleamic acids and amines. For the maleamic acids, the signals of the allylic protons were shifted downfield as the concentration decreased. In the case of the free amines, the signals of the protons in proximity of the nitrogen atom (one or two

bonds away) were shifted upfield upon dilution (Figures S12–S17). These observations are consistent with the formation of an ion pair: there is a second equilibrium after the formation of the maleamic acids where they donate a proton to a second amine molecule. As expected from an acid-base reaction, at high concentrations the equilibrium is shifted towards the proton transfer, while at lower concentrations it is more favourable that the two molecules remain neutral.

Since the formation of maleamic acids requires the amine to be able to act as a nucleophile, we predicted that we could also control the equilibrium by addition of a Brønsted acid - which would protonate the amine and shift the equilibrium away from amide formation. To prove this, we prepared maleamic acid **1'**, by mixing dimethylmaleic anhydride and diethylamine in the conditions previously described, and added enough TFA to it to protonate all of the amine. As expected, this shifted the equilibrium completely towards anhydride and protonated amine. After this, by adding an excess of triethylamine to neutralize the TFA, the initial concentration of maleamic acid was completely restored. We repeated this cycle four times, switching between >97% and <2% of amide **1'** (Figures 1b and S18), without any loss of conversion due to the accumulation of salt.

Once that we established that maleamic acids were in equilibrium with their respective anhydrides, we decided to test their reactivity towards amide exchange. For that, we prepared maleamic acid **1'** as described above, by mixing dimethylmaleic anhydride and two equivalents of diethylamine (**1**), and added another two equivalents of dipropylamine (**2**) to the mixture. Exchange proceeded, and in 24 h the library reached a composition of roughly equal amounts of **1'** and **2'** (Figure 2a). In order to test that this distribution corresponded to the thermodynamic equilibrium, we performed a dual point entry experiment: preparing in this case maleamic acid **2'** first and adding diethylamine in second place. The same composition was reached in both cases regardless of the starting point (Figures 2b and 2c), confirming that this distribution corresponds to the thermodynamic minimum.

Next, we decided to study the scope of the transamidation reaction, by preparing maleamic acids from amine **1** and different anhydrides, and adding amine **2** to observe the exchange between them. We monitored the spectral region corresponding to the CH_2 protons next to the nitrogen atom for 60 h, observing only equilibration of the library for the maleamic acid prepared from dimethylmaleic anhydride. Spectral changes were also observed in the maleamic acids prepared from 3,4,5,6 - tetrahydroterephthalic and diphenyl anhydrides, although to a lesser extent; and no transamidation was observed in maleamic acids derived from maleic, dichloromaleic, or phthalic anhydrides (Figure S19). These results follow the trend described previously for the hydrolysis of these compounds, where the reaction rate is determined by the effective molarity (EM) of the carboxylate in the proximity of the amide.[37] As in that case, the dimetyl-substituted maleamic acid (EM $= 3 \times 10^{13}$ M) reacts faster than its 3,4,5,6 - tetrahydrophthalic analogue (EM $= 1 \times 10^{12}$ M), and even faster than the maleamic acids derived from maleamic anhydride (EM $= 2 \times$

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doi.org/10.1002/chem.202201043

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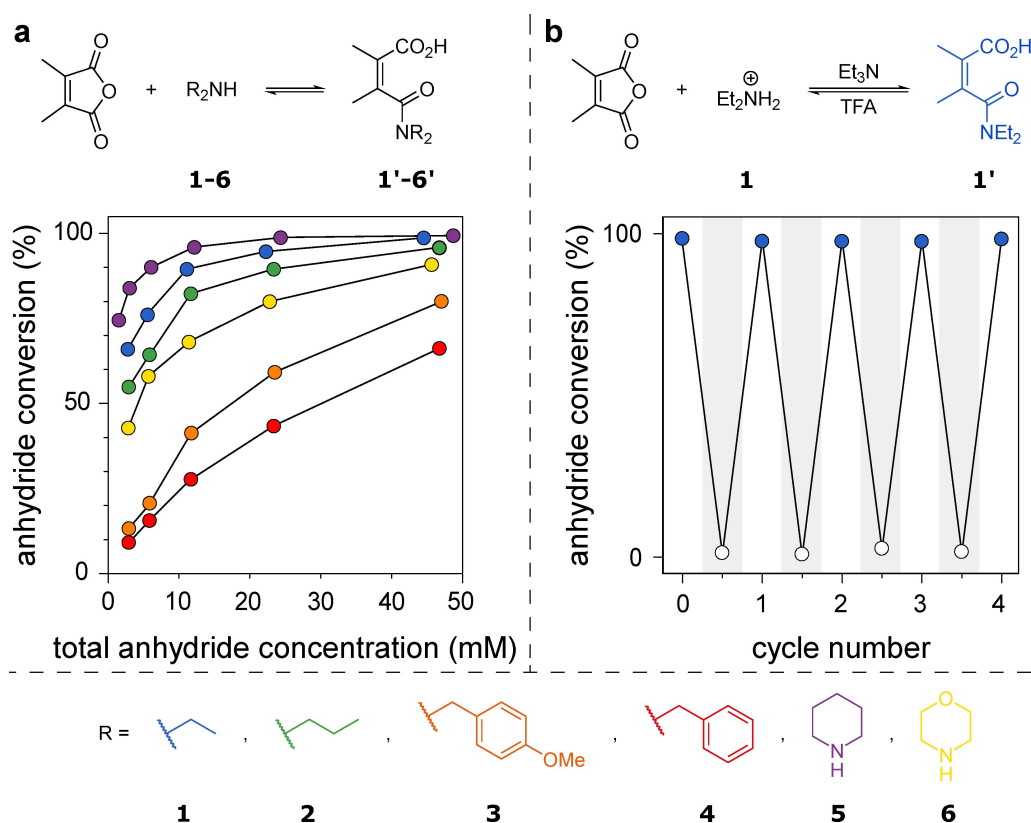European Chemical
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Figure 1. Reversible and switchable amide formation between dimethylmaleic acid and different secondary amines. a) Effect of total concentration on the conversion to maleamic acid. Equilibrated solutions containing mostly maleamic acids **1′-6′** ([anhydride]$_t$ ≃ 48 mM in CD$_3$CN, 2 equiv. amine) were subjected to a series of dilutions with more CD$_3$CN, leading to a shift in the equilibrium back to the amine and anhydride precursors in all cases. b) Switching between maleamic acid and anhydride + amine by addition of a Brønsted acid. The composition of a solution of dimethylmaleic anhydride (37 mM) and diethylamine (84 mM) was switched repeatedly between maleamic acid and protonated amine + anhydride by additions of TFA and triethylamine. In the first step, 87 mM of TFA were added to completely protonate the amine, and in the following cycles a small excess of both TEA and TFA was added until the equilibrium had shifted completely.

10^9 M) and phthalic anhydride (EM < 1.7 × 10^9 M), which did not react noticeably on this time scale.

The scope of the transamidation was broader when changing the substitution of the nitrogen atom. We tested this by preparing maleamic acids from dimethylmaleic anhydride and the amines **1–6**, and testing individually the exchange between each of them and the other 5 amines for a total of 30 amide-amine combinations (Figures S20–S26). We observed transamidation in most of the cases, leading to an equilibrium distribution of amides (as demonstrated by dual point entry experiments – the final spectra were always identical regardless of the starting point of the exchange). The only exceptions were the two reactions involving both **5** (piperidine) and **6** (morpholine), since their initial spectra were already too similar to observe any changes as transamidation progressed. However, since these amines and their respective maleamic acids show transamidation when combined with all the others, we expect that exchange takes place between them as well, although we cannot categorically confirm it by ^{1}H-NMR.

Naturally, the final composition of these two-amide libraries will depend on thermodynamic parameters: the stability of the two maleamic acids, and the leaving group ability and basicity

of their corresponding amines. However, before reaching equilibrium, the libraries might pass through a different composition that would be dictated by kinetic parameters instead – such as the different nucleophilicities of the two amines. We found this to be the case in libraries prepared by mixing dimethylmaleic acid and amines **1** and **3** (Figure 3a). Even though both amines were added simultaneously to the library, we observed an initial fast formation of **1′** followed by a slow displacement by **3**. This displacement was accelerated by lowering the total concentration of the library and the ratio between amines and anhydride, and led to an equilibrium composition dominated by **3′** (Figure S27). By tuning the ratio between amines, we could accentuate the difference between kinetic and thermodynamic distributions even further and obtain a transient wave of **1′** that was followed by an almost complete replacement by **3′** (Figure 3b). This level of temporal control, allowing us to access kinetic compositions in a library before it transitions to the thermodynamic equilibrium, is a feature recognised as critical for the future development of DCC.[45]

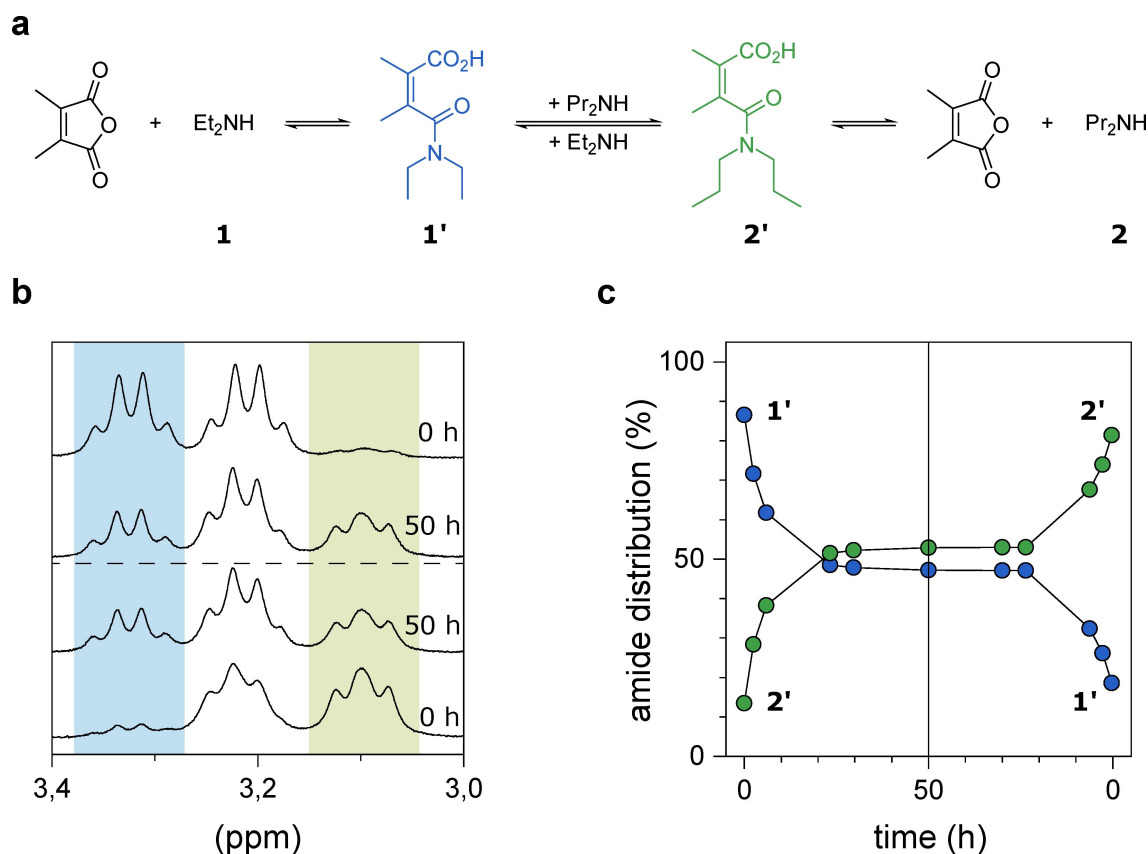During the optimization of initial conditions for these libraries, we noticed that the kinetics of the system were

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doi.org/10.1002/chem.202201043

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Figure 2. Dual point entry experiment for transamidation in maleamic acids. a) Amide exchange reaction between **1′** and **2′**. b) ^{1}H-NMR spectral data showing the transamidation progress. Only the region corresponding to the CH$_2$ protons next to the nitrogen atom is shown. The top half of the graph corresponds to the exchange from **1′** to **2′**, and the bottom half to the reverse reaction. The top and bottom spectra correspond to the reaction immediately after addition of the second amine and the ones in the middle to the reaction after 50 h. The highlighted areas were integrated to calculate the percentages shown in panel c. c) Composition of amide libraries over time. Blue circles correspond to **1′**, and green circles correspond to **2′**. The left side of the graph corresponds to the **1′**→**2′** exchange, and the right side to the reverse reaction. At 50 h, both reactions have converged to the same composition (center).

drastically affected by changes in the initial ratio between amines and anhydride. This can be observed in Figure 3c, which shows the composition after 24 h of libraries prepared from a constant concentration of dimethylmaleic anhydride and growing concentrations of amines **1** and **3** (in a 1:1 ratio to each other). At low amine concentrations (less than two equivalents), the libraries converged on a composition dominated by amide **3′**, in a ratio of approximately 7:3 compared to **1′**. This distribution did not change over time, indicating that it corresponded to the thermodynamic minimum. At higher concentrations of amines (more than two equivalents), the observed library compositions were initially dominated by **1′**, but they slowly drifted towards the formation of more **3′** (Figures 3d and S28). Libraries in this kinetically trapped state took a remarkably long time to equilibrate (some of them over two months), so the exact equilibrium composition could not be determined, although it approached the 7:3 ratio observed in libraries with a lower amines:anhydride ratio. Therefore, we deemed this observation to be the result of a kinetic effect: increasing the ratio between amines and anhydride did not seem to affect the equilibrium composition of the libraries, but

it drastically changed their equilibration time, from less than a day to more than two months.

This unusual behaviour can be explained by considering that there is no direct reaction between **1′** and **3′**, and exchange takes place through two separate equilibria between dimethylmaleic anhydride and the amines **1** and **3** (Figure 3a). It is well known that maleamic acids do not react to form their corresponding anhydride and amine unless the carboxylic acid in β-position is protonated[34–37] (as the proton needs to be transferred to the amine for it to be a suitable leaving group), so exchange will be slowed down by the deprotonation of that acid. In the libraries described here, set up in acetonitrile, these groups can only be deprotonated by the amines **1** and **3**, which act both as nucleophiles and as bases. At low amine concentrations, there are not enough amine molecules to form the maleamic acid and completely deprotonate it, so some protonated maleamic acid molecules remain and exchange can take place through them. In contrast, at concentrations higher than two equivalents, there are enough amines to convert all anhydride to maleamic acid, and to fully deprotonate it, forming an ion pair with it. The lack of available -COOH groups then prevents the amine from leaving and the amide bond
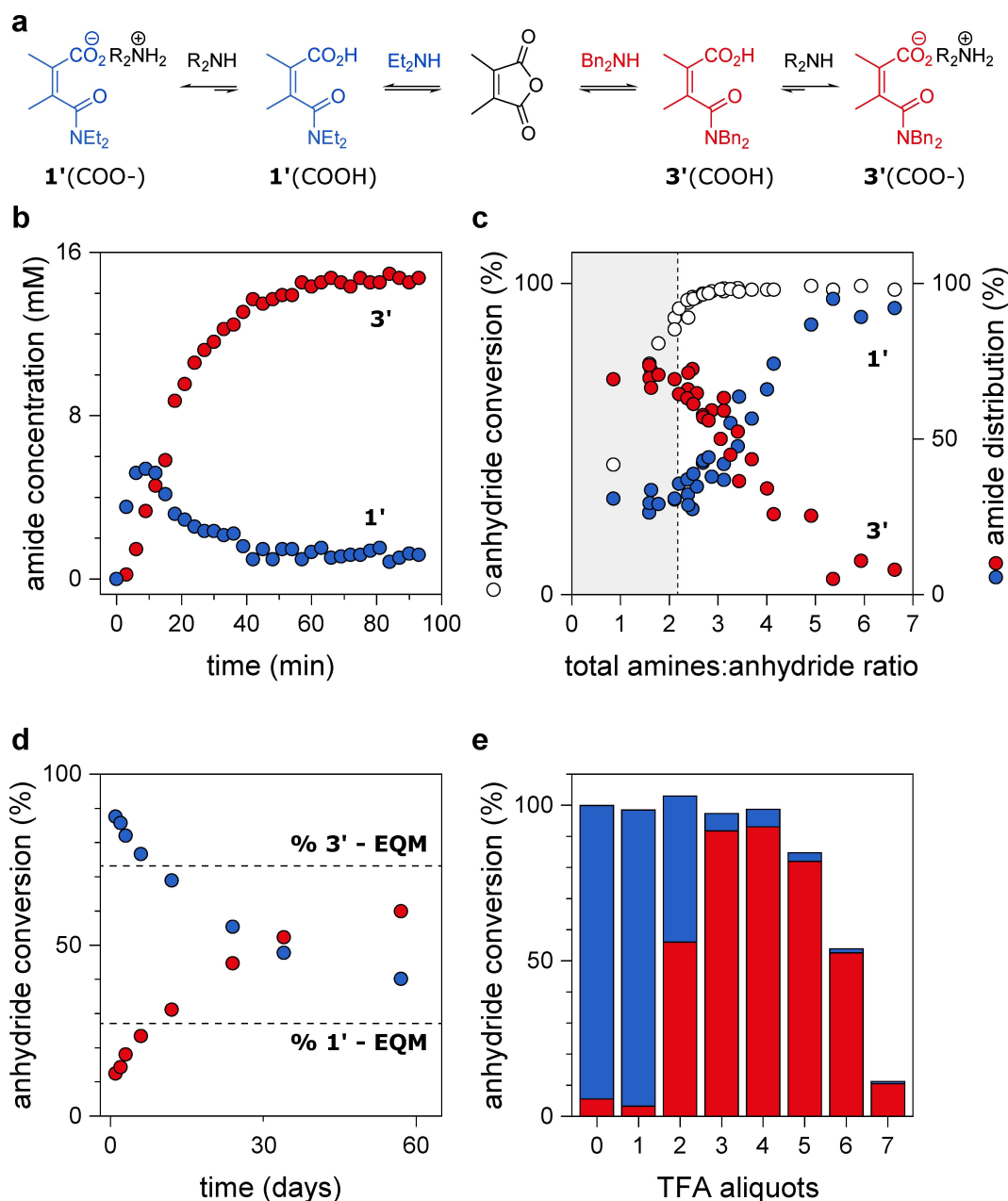
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doi.org/10.1002/chem.202201043

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Figure 3. a) Proposed mechanism for amide exchange in libraries formed from dimethylmaleic anhydride, diethylamine, and dibenzylamine. b) Transient formation of **1'** followed by displacement by **3** in a library containing 24 mM of dimethylmaleic anhydride, 9.4 mM of diethylamine and 33 mM of dibenzylamine. c) Composition after 24 h of libraries prepared from dimethylmaleic anhydride (40 mM), diethylamine and dibenzylamine in varying concentrations. The ratio between the two amines was kept 1:1 in all cases. The grey region indicates the libraries where the conversion of anhydride (open circles) was lower than 90%. d) Evolution over time of a library prepared as in panel c, with a ratio amines:anhydride of 5.9:1. The dotted lines represent the average conversions found in equilibrated samples at lower amine:anhydride ratios. e) Composition after 24 h of libraries prepared from dimethylmaleic anhydride (39 mM), diethylamine and dibenzylamine (4.8 equivalents each), after addition of different amounts of TFA. Each aliquot of TFA corresponds to 4 μL (52 mM).

remains stable, which prevents exchange and favours the kinetic product (in this case, **1'**).

Following this hypothesis, we were able to control the composition of kinetically trapped libraries of **1'** and **3'** (containing >90% of **1'**) by protonating the maleamic acids using TFA (Figure 3e). We were able to obtain four "states" with different compositions depending on the amount of TFA added. With low concentrations of TFA, the exchange reaction was not

significatively accelerated, and the libraries remained in the kinetic trap (points 0 and 1). With higher concentrations of TFA, the library equilibrated faster, reaching a composition with significant amounts of both amides (point 2). The composition of this library differed slightly from the equilibrated ones shown in Figure 3b, most likely as an effect of the acid. The addition of higher concentrations of TFA led to a selective protonation of **1** over **3** (due to their different basicities), which in turn led to

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doi.org/10.1002/chem.202201043

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libraries containing practically only **3'** (points 3 and 4). Finally, upon addition of even larger amounts of TFA, **3** became also protonated and not available for amide formation, which led to lower anhydride conversions until barely any amides were left (points 5–7).

Conclusion

In conclusion, here we describe reversible transamidation in maleamic acids, a class of compounds with properties that have been known for over 70 years, but with a considerable potential for dynamic combinatorial chemistry that has been previously unnoticed. Unlike most of the transamidations that have been described in the past, this reaction does not require harsh conditions or the addition of external catalysts, and proceeds readily in acetonitrile at room temperature. The exchange takes place in this case through the anhydride that is in equilibrium with the maleamic acids, and therefore its rate is accelerated by conditions where the equilibrium favours anhydride formation: low concentrations, low amine:anhydride ratios, and anhydrides with a substitution pattern that enhances a high effective molarity of the carboxylate next to the amide bond all contribute to promoting the exchange reaction described here.

This anhydride-mediated mechanism also allows us to control the reaction very precisely. By tuning the preparation conditions, we can easily obtain libraries that either equilibrate in a matter of hours or remain in a kinetic trap for months. In addition, we can further manipulate the libraries by adding a Brønsted acid in order to accelerate exchange, change the library distribution, or even prevent amide formation alto-gether.

Despite the substrate limitations that are inherent to the mechanism, we believe that this reaction can easily lead to libraries with a high number of compounds: by using asymmetric anhydrides and amines, the number of possible library members grows rapidly, as each maleamic acid can have up to four possible regioisomers. These reaction should also allow access to a feature that is normally hard to achieve in amides: transient formation. By mixing water with the organic solvent in which exchange takes place, hydrolysis should become a (practically) irreversible destruction pathway that would compete with transamidation. We predict that the combination of transient formation designed in this way with structural components that favour self-assembly (the carbox-ylate moiety already makes the structure resemble an amphi-phile) should lead to the out-of-equilibrium formation of structures, which would only persist for as long as new anhydride is re-formed or added. We believe that the combina-tion of these two factors, the ability to access kinetic and thermodynamic regimes in a controlled way, and the use of a type of bond normally unavailable for reversible reactions make maleamic acid libraries a substantial addition to the toolbox of dynamic combinatorial chemistry, both at equilibrium and out of equilibrium.[46]

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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