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AUTOCATALYSIS AND ORGANOCATALYSIS WITH KEMP'S TRIACID COMPOUNDS

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Abstract – Synthetic structures capable of autocatalysis based on molecular recognition – self-replication – were introduced nearly 20 years ago. These systems involved neither informational oligomers such as nucleic acids nor conditions that are generally regarded as prebiotic, but they revealed how self-complementary molecules could act as templates for their own formation and helped define the structure of minimalist replicators. Recent expansions in the field of organocatalysis raise the possibility that a synthetic structure might behave as an autocatalyst *and* function as a chemical catalyst for other reactions. We show here that these properties can be engineered into a single synthetic structure: the compound can selectively accelerate its own formation and catalyzes hydrogenation reactions of nitrostyrene. It is likely that a wide variety of synthetic structures can be modified for autocatalysis and organocatalysis.

INTRODUCTION

The unusual structure of Kemp's triacid[1] **1a** (Figure 1) offers advantages in chemical studies of molecular recognition[2] and replication.[3] The initial synthetic compound that showed autocatalysis based on recognition[4] was the derivative **2**, a structure that comprises adenine covalently bound to a receptor for adenine. This self-complementary feature allowed **2** to act as a template for its own formation by recognizing both components from which it is made as in **3**.[5]

Earlier, in 1986 a hexameric, self-complementary DNA strand was shown to self-replicate[6] and the same behavior was engineered into an RNA molecule 15 years later.[7] The catalytic activity of RNA in other reactions had already emerged, discoveries which led to the postulation of an "RNA world",[8] where ribozymes functioned both as carriers of genetic information and performed the catalysis and regulation

of reactions required in metabolism. Studies of the replication of simple organic molecules led to the many types of self-replicating structures[9] presently known, including peptides.[10] Yet these explorations did not lead to systems that were informational in the sense of containing a sequence that could be evolved, or to compounds that catalyzed reactions other than their own formation (or that of very closely related structures[11]). This latter shortcoming prompted the present research – the search for synthetic molecules that act as both catalysts and autocatalysts. While we make no claims that such compounds or conditions we use are conventionally prebiotic, we intend to show, through chemistry, that "autocatalytic reproduction of catalytic capabilities"[12] as proposed by Eschenmoser is a attainable goal, and one that should be included in a definition of the chemistry at life's origins. Recently we provided evidence that synthetic structures based on a xanthene skeleton act as both autocatalysts and organocatalysts when imidazolidinones[13] or thiourea[14] functions are embedded within them. Here we report the adaptation of a replicator based on Kemp's triacid and its characterization as an autocatalyst and an organocatalyst.

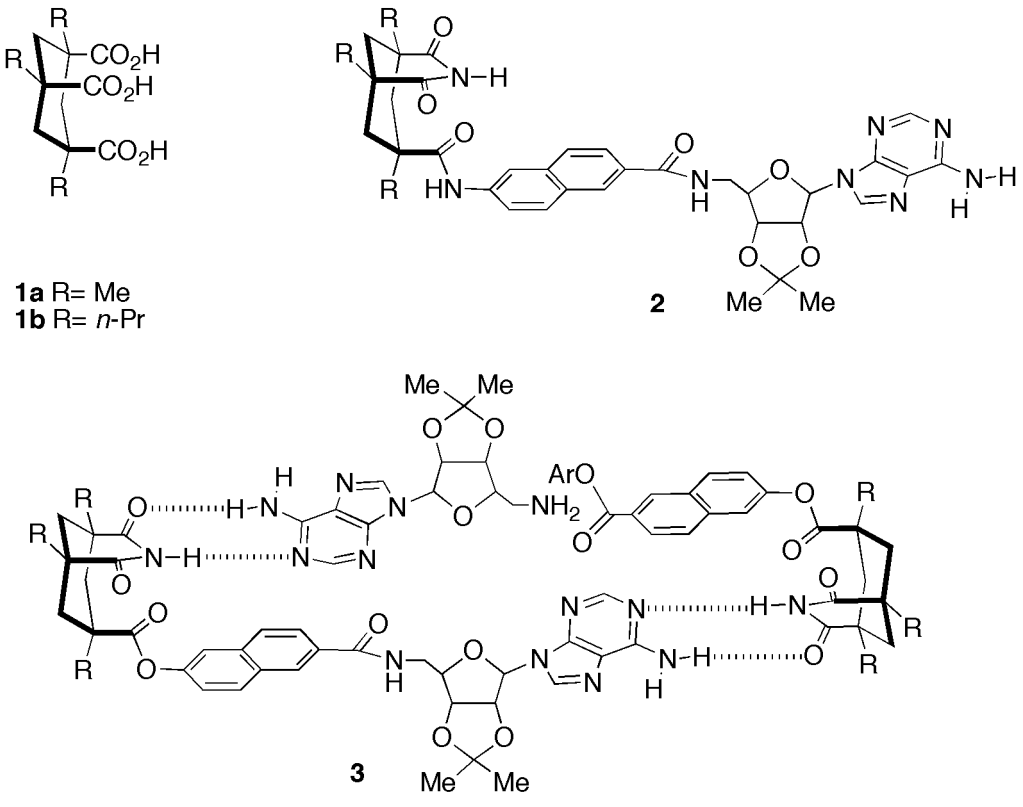
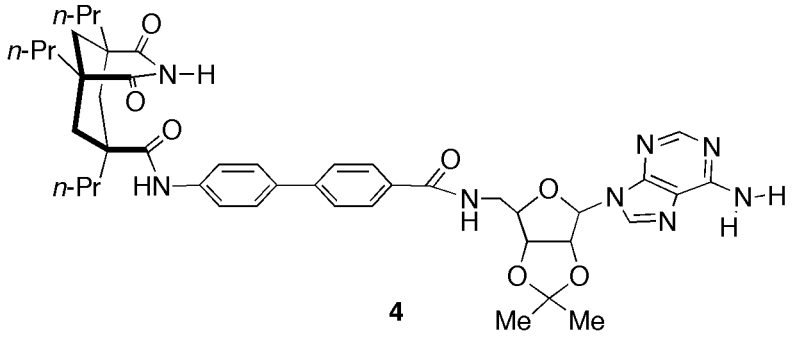


Figure 1. Line drawings of Kemp's triacids **1**, the previously reported autocatalytic molecule **2**, and proposed self –replication mechanism

RESULTS AND DISCUSSION

We chose to make modifications to a replicator **4** (Figure 2) that showed modest sigmoidal kinetic behavior[15] and bearing a biphenyl spacer between the recognition sites (the imide and adenine). The

minor intrusions on the structure leading to compound **5** – an amide linkage of the biaryl to the Kemp's triacid, the substitution of a thiourea for the amide and the introduction of a nitro group to enhance the acidity of the thiourea – were not expected to interfere with the recognition elements involved in replication. The peripheral propyl groups of the Kemp's triacid are there merely to improve its solubility in organic solvents.



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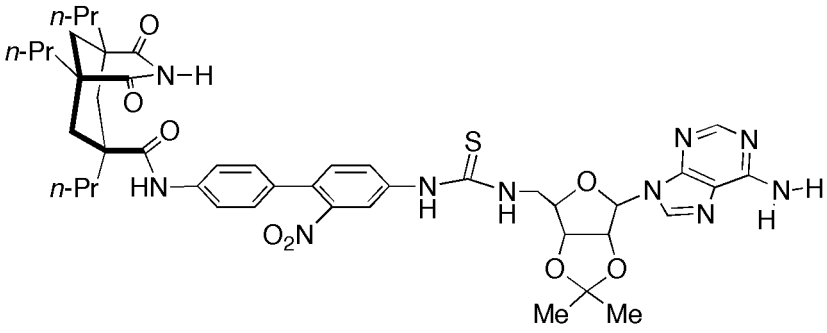

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Figure 2. The previously reported self-replicator **4** is modified to contain an embedded thiourea site in **5**

The synthesis was uneventful and is outlined in Figure 3. Isothiocyanate **9a** was generated from aniline **8** and proved to be very reactive to amine nucleophiles, a feature that posed some challenges for its characterization as a replicator. Specifically, the adenosine amine **10** gave the thiourea **5a** on brief exposure (a few minutes) to **9a** at ambient temperature. Following this reaction in real time by conventional kinetic methods using NMR or HPLC was not possible, so we considered competition experiments instead. In these experiments nucleophiles and electrophiles without recognition elements compete with those involved in the intended autocatalysis reaction. The product ratios were determined by HPLC based on integration of corresponding adsorption signals at 254 nm.

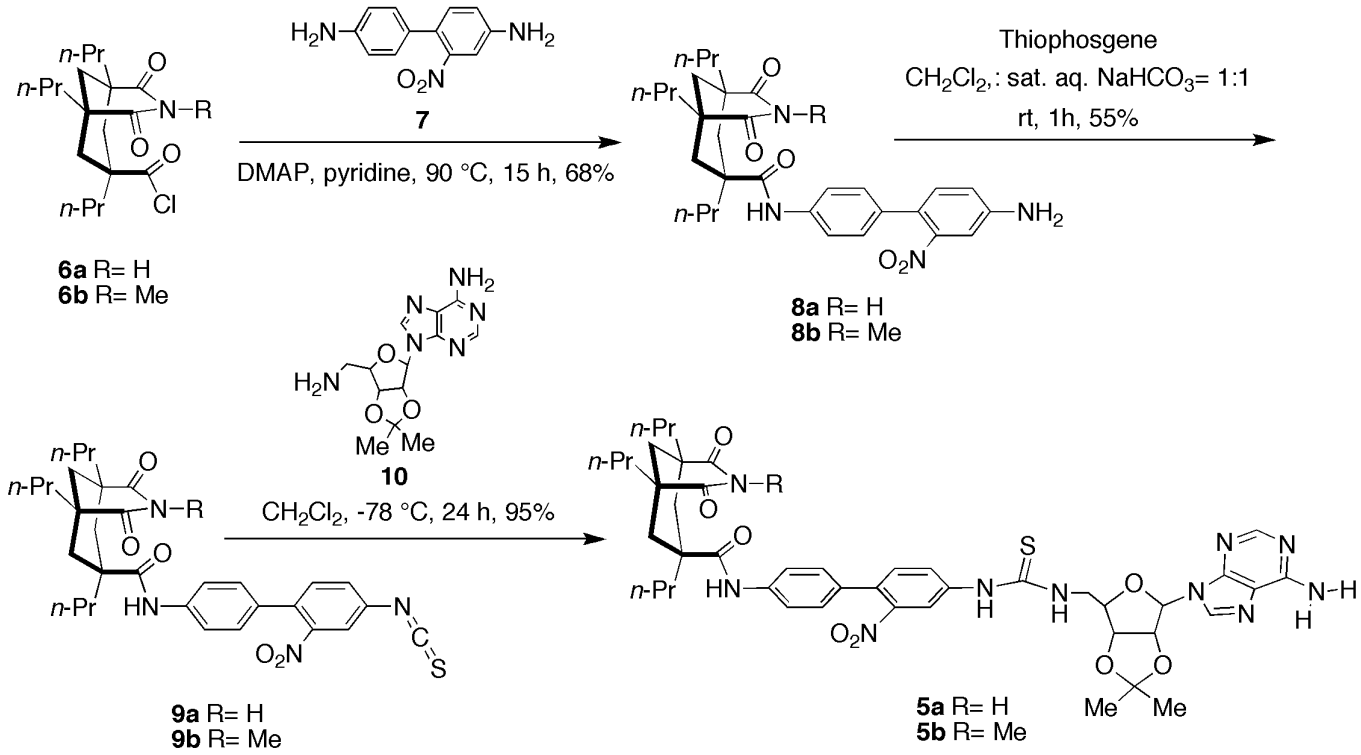
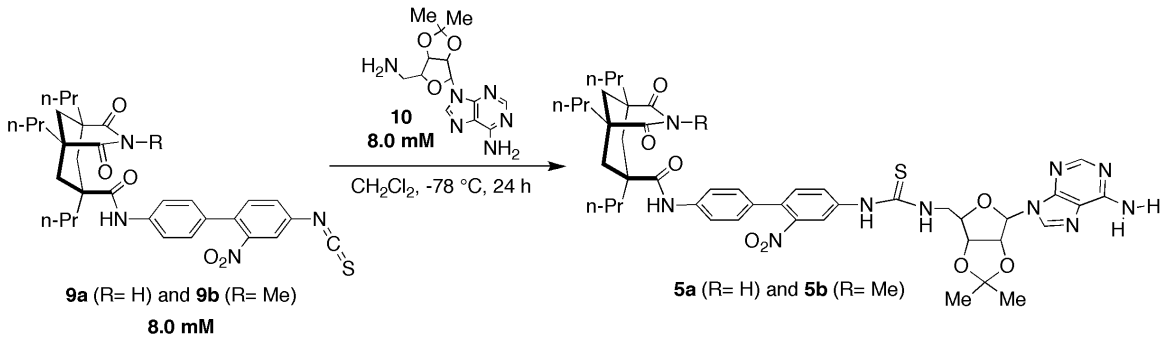


Figure 3. The synthesis of autocatalytic and organocatalytic molecules

First, an electrophile lacking the imide recognition element was prepared to compete with **9a**. This involved *N*-methylation of the imide function as in **9b** at a site some distance from the isothiocyanate function undergoing reaction. The competition of **9a** and **9b** for a limited amount of adenosine amine **10** showed that the thiourea **5a** *was formed in greater amounts* (thiourea **5a**: *N*-methylated thiourea **5b** = 62:38). When thiourea **5a** was present at the beginning of the competition reaction, the preference increased by a small but measurable degree (Entry 2, 67:33, and Entry 3, 72:28, Table 1). Apparently, **5a** was able to act as a template for its own formation. On other hand, when thiourea **5b**, which is unable to act as a template for its own formation, was present at the beginning of the competition reaction, the product ratios did not change. In short, these results indicated that molecular recognition at the imide group was involved in the reaction and **5a** enhanced its own formation, acting as an autocatalyst.

Table 1



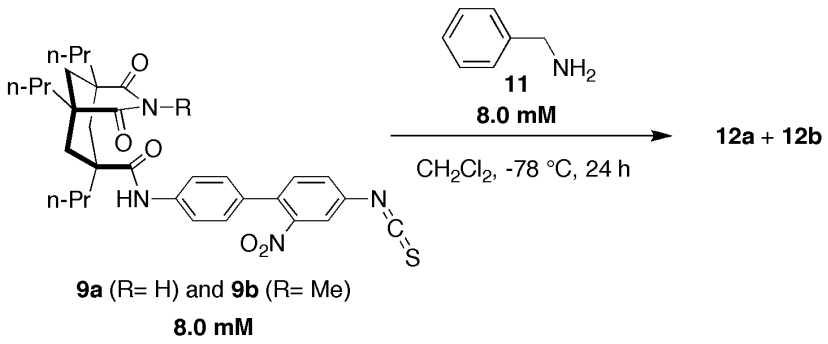
Entry	Catalyst (%)	Yield of **5a** + **5b** (%)[a]	Ratios (**5a** : **5b**)[b]
1	**5a** (0)	95	62 : 38
2	**5a** (25)	93	67 : 33
3	**5a** (50)	94	72 : 28
4	**5b** (25)	91	60 : 40
5	**5b** (50)	94	61 : 39

a) Isolation by column chromatography. b) Ratios were determined by HPLC peak area (254 nm) after column chromatography.

[a] Isolation by column chromatography. [b] Ratios were determined by HPLC peak area (254 nm) after column chromatography.

Second, competition experiments of **9a** and **9b** with benzyl amine **11** (a nucleophile that lacks a recognition site) show no preference between the two thioisocyanates, as shown in Table 2. No template effect is observed: products **12a** and **12b** are not autocatalysts.

Table 2



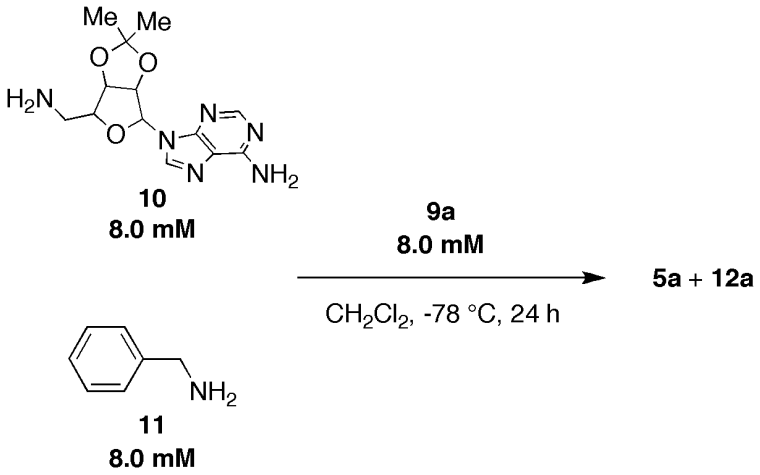
Entry	Catalyst (%)	Yield of **12a** + **12b** (%)[a]	Ratios (**12a** : **12b**)[b]
1	(0)	95	48 : 52
2	**5a** (25)	96	49 : 51
3	**5b** (25)	98	50 : 50

a) Isolation by column chromatography. b) Ratios were determined by HPLC peak area (254 nm) after column chromatography.

[a] Isolation by column chromatography. [b] Ratios were determined by HPLC peak area (254 nm) after column chromatography.

Finally, competition experiments of adenosine amine **10** and benzyl amine **11** for the *N*-methyl imide thioisocyanate **9b** (lacking a recognition site) showed a preference for nucleophilic attack by amine **10** (**5b**:**12b** = 62:38; c.f. Entry 1 in Table 3 **5a**:**12a** = 70:30). Recognition notwithstanding, adenosine amine **10** is the better nucleophile in this reaction system. Taken together, these results show that autocatalysis based on molecular recognition – replication – takes place during the formation of thiourea compound **5a**, albeit to a modest extent.

Table 3



Entry	Catalyst **5a** (%)	Yield of **5a** + **12a** (%)[a]	Ratios (**5a** : **12a**)[b]
1	0	93	70 : 30
2	25	92	74 : 26
3	50	94	81 : 19

a) Isolation by column chromatography. b) Ratios were determined by HPLC peak area (254 nm) after column chromatography.

ORGANOCATALYSIS

The solvents and temperatures that favor hydrogen bonding between molecules are essential for the recognition involved in self-replication and these conditions are also typical for organocatalysis by thioureas. There is a subtle difference in the two applications: The kinetics of autocatalytic reactions of the sort discussed above are often seen to obey the "square root law".[16] Since the product (i.e. catalyst) is to varying degrees a hydrogen-bonded dimer, the rate enhancements are proportional to the concentration of the free monomer, a value related to the square root of the total concentration. The dimers are generally not autocatalysts – and product inhibition is inevitable – but the dimers can be organocatalysts if the participating functional groups are exposed to the reagents undergoing change.

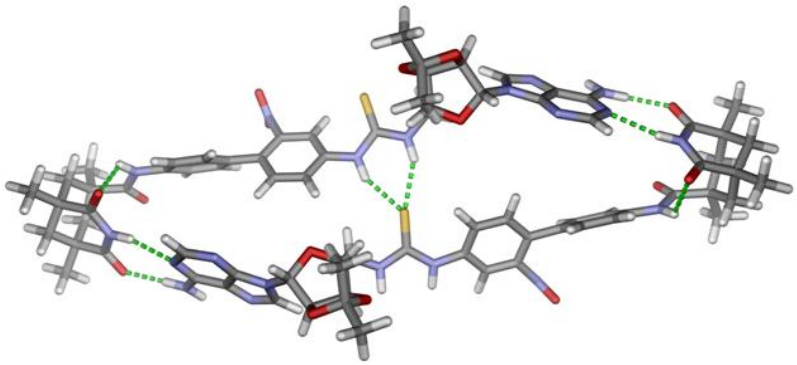


Figure 4. The DFT (B3LYP) energy-minimized dimeric structure

There is evidence that **5a** is highly dimerized at the low temperatures of the replication experiments, and hydrogen bonding may occur between the very thioureas that are required for organocatalysis as shown in 12 (Figure 4). This hydrogen bonding still leaves an open thiourea site that could even be more activated in H-bonding catalysis than the corresponding monomer,[17] but will most likely suffer from steric hindrance due to the congested environment in which it resides. Since there is no requirement that the two functions – catalysis and autocatalysis – need to be optimal, or even operational, under the same conditions, the higher temperatures more appropriate for the organocatalytic applications were used. The thiourea site in the self-replicating molecule **5a** is capable of acting as a catalyst through hydrogen bonding to the transition state of various reactions such as cycloadditions,[18] condensations,[19] hydrocyanations,[20] Strecker,[21] and Mannich[22] reactions, especially in asymmetric settings.[23] The acidity of the thiourea is of paramount importance to the rate acceleration; electron-withdrawing groups adjacent to the thiourea function are known to enhance its hydrogen donor ability and consequently its catalytic activity.[23] The nitro group was inserted into the biphenyl structure for just this reason. Three reactions were studied to assess the organocatalytic activity of the thiourea function in **5a**: Michael additions, Friedel-Crafts alkylation, and a hydrogen transfer reaction. The results of the organocatalytic experiments are reported in percent yield after a constant time for each reaction discussed.

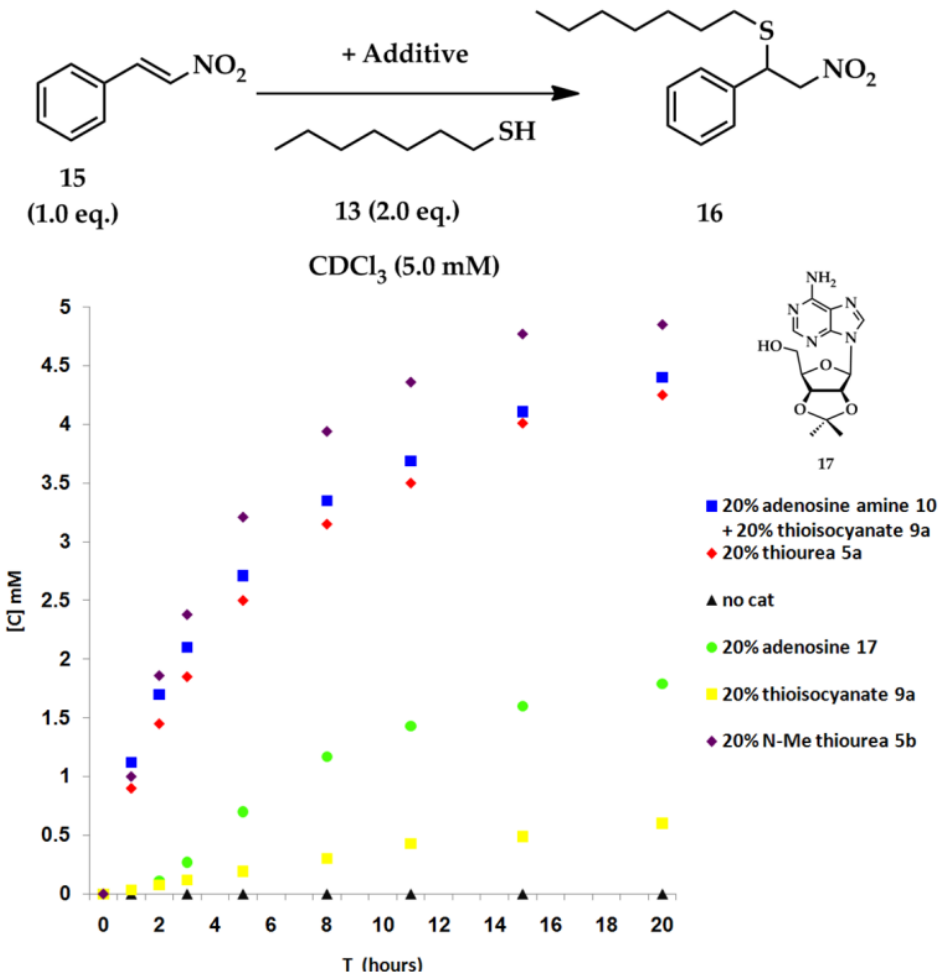


Figure 5. Effects of catalysts on the Michael addition using 1-heptanethiol as a nucleophile

The organocatalytic activity of **5a** was demonstrated in Michael additions using 1-heptanethiol **13** and 2,4-pentanedione **14** as nucleophiles. Compound **5a** was an effective catalyst for the addition of 1-heptanethiol **13** to nitrostyrene **15** and gave the adduct **16** in 85% yield (Figure 5). Control experiments were performed to evaluate the organocatalytic activity of other functional groups embedded in **5a** such as the imide group and the heterocycles of the adenosine. Because Michael additions are known to be catalyzed by bases, we used the adenosine alcohol **17** as a control instead of amine **10**. Catalytic amounts of 17 gave a 35% yield of product **16** under the same conditions. Thioisocyanate **9a** was also used as a control and gave only 12% product. While these results show that the catalytic activity of **5a** is not exclusive to the thiourea function, it is certainly the dominant factor for catalysis.

Additional experimentation indicated that the organocatalytic ability of **5a** is decreased by its dimerization (see Figure 4) under these conditions. *N*-methylated thiourea **5b**, which is unable to dimerize, showed *higher* organocatalytic ability (Figure 6, purple points vs. red points). The combination of thioisocyanate **9a** and aminoadenosine **10** showed the same activity as thiourea **5a**, illustrating that the thiourea formation is much faster than the thiol addition.

Compound **5a** was tested as a catalyst in another Michael reaction. The addition of 2,4-pentanedione **14** to nitrostyrene **18** as catalyzed by **5a** gave **19** in 63% yield (Figure 6). However, the same product was observed with the amine **10** (42% yield) and even with the isothiocyanate **9a** (45% yield). Apparently, a thiourea is not required for catalysis of this reaction, and what little organocatalytic activity this function shows in **5a** must be decreased through its dimerization to **12**. The n-methyl imide 5b showed, again, the best activity (Figure 6; compare the purple and red data points), while the combination of thioisocyanate **9a** and aminoadenosine **10** showed the same activity as thiourea **5a**.

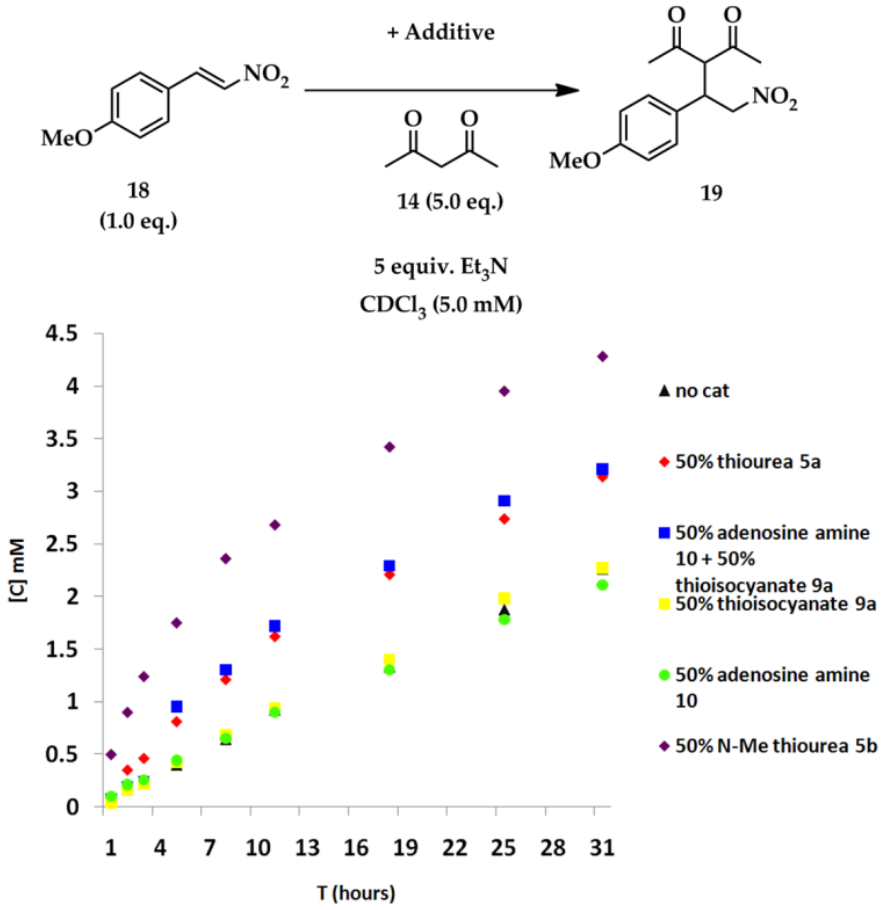


Figure 6. Effects of catalysts on the Michael addition using 2,5-pentanedione as a nucleophile

Finally, the organocatalytic activity of **5a** was demonstrated in transfer hydrogenation using the Hantzsch ester **20** as the hydride source. *Trans*-β-nitrostyrene **15** was reduced in high yield (80% of **21**) at 35°C using **5a** (Figure 7). In the absence of **5a** only a small amount of reduction was observed (14% of **21**). The yields with the thioisocyanate **9a** (28%), the amine **10** (47%) and alcohol **17** (29%) showed that other functional groups do participate in this reaction. The imide of the Kemp substructure can catalyze the reduction in an estimated 14% yield after 6 days (28%-14% = 14%) and the adenosine group can do likewise in about 15% yield (29%-14% = 15%). From these estimates, the organocatalytic activity of the thiourea group **5a** accounts for about 51% [80%-(14%+15%)=51%] of the product. As in the other

reactions, dimerization of **5a** decreases its organocatalytic activity (Figure 7; compare purple and red data points), and the combination of thioisocyanate **9a** and aminoadenosine **10** shows activity indistinguishable from the intact thiourea **5a**.

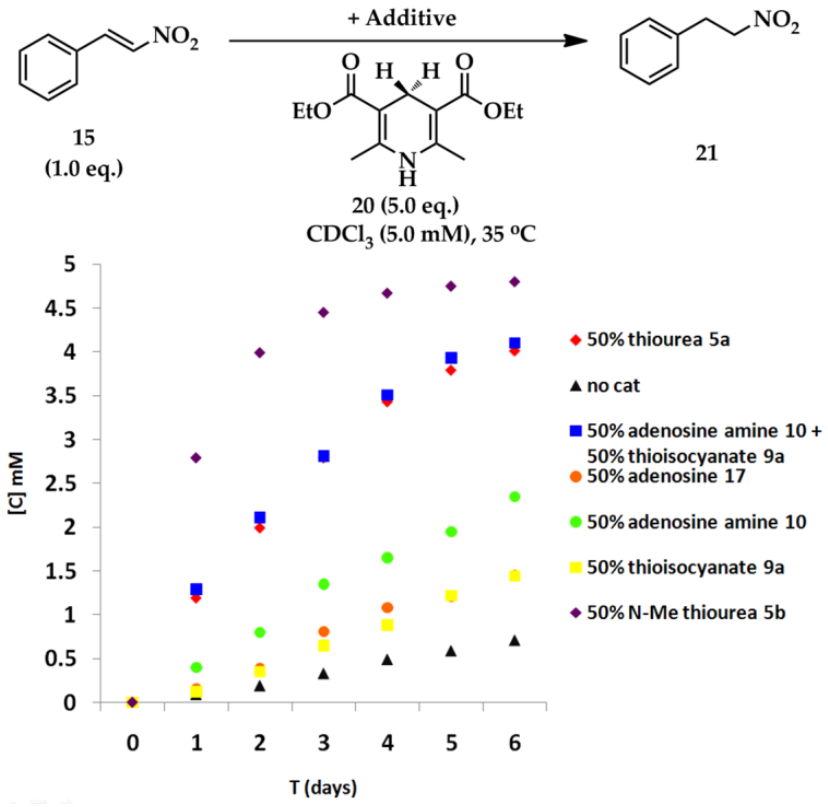


Figure 7. The organocatalyzed reduction of a nitro-olefin

CONCLUSION

The new synthetic compound **5a** shows the earmarks of a self-replicating system: recognition-based autocatalysis. This was established through competition experiments with structurally related compounds lacking the recognition features (hydrogen bonding sites). The self-replicator, however, showed only modest organocatalytic activity in all three reactions examined. Its tendency to form a dimeric structure in organic media is held responsible for this shortcoming, since the n-methylated thiourea **5b**, which is unable to dimerize, consistently showed higher activity as an organocatalyst. In the future, one way of enhancing catalytic action could be to introduce complementary functions that compete for the hydrogen-bonding sites into the substrates of the reaction. For example, appropriate placement of a purine nucleus of adenine on either partner of the Michael addition reaction should promote catalysis by **5a**, and could introduce selectivity into the process. For the present, we suggest that molecules such as **5a** provide capabilities of replication and chemical catalysis as minimalist vehicles of "genetics" and "metabolism", respectively. These functions are widely acknowledged[24] as required

for molecules nearer to the origin of life than, say, RNA. As for the distant past, the potential precursors to the RNA world are shrouded in mystery but new candidates are emerging from chemical synthesis.[25,26] The search is expanding as even water is no longer regarded as a required solvent.[27]

EXPERIMENTAL SECTION

Aniline **8a**: Acyl chloride **6** (280 mg, 0.819 mmol), 3-nitro-4,4'diaminobiphenyl **7** (209 mg, 0.901 mmol), and a catalytic amount of DMAP (10 mg) were added to a 50 mL round bottom flask equipped with a reflux condenser and a stir bar. The reaction was placed under an atmosphere of argon and 30 mL of dry pyridine was added. The reaction mixture was heated to 90 °C for 15 h. The reaction mixture was then cooled to room temperature and the solvent was removed under reduced pressure. The residue was purified using column chromatography eluting with CH_2Cl_2 and a gradient of EtOAc to a final mixture of 5% EtOAc in CH_2Cl_2 giving a red solid. Yield 302 mg (68%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.28 (s, 1H), 7.16 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.4 Hz, 1H), 7.08 (d, *J* = 2.3 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 4.03 (s, 2H), 2.59 (d, *J* = 14.3 Hz, 2H), 2.22 (d, *J* = 13.2 Hz, 1H), 2.01 – 1.92 (m, 1H), 1.50 (m, 2H), 1.42 – 1.19 (m, 12H), 0.94 (t, *J* = 7.1 Hz, 6H), 0.86 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 176.3, 171.4, 149.8, 146.7, 136.6, 134.2, 132.8, 128.7, 125.4, 121.1, 118.7, 109.8, 48.3, 46.5, 43.3, 43.2, 40.2, 37.8, 17.2, 17.1, 14.7, 14.5; HRMS (MALDI-FTMS: MH^+) calcd. for $C_{30}H_{38}N_4O_5^+$ 535.2915, found 535.2911.

Thioisocyanate **9a**: Aniline **8a** (152 mg, 0.280 mmol) was added to a 100 mL round bottom flask and dissolved in 20 mL CH_2Cl_2. A saturated aqueous solution of sodium bicarbonate (20 mL) was added and the biphasic mixture was cooled to 0 °C in an ice bath. Thiophosgene (327 mg, 2.80 mmol) was added dropwise to the vigorously stirred mixture. The reaction mixture was then allowed to warm to room temperature for 1 h. The organic phase was separated and concentrated under reduced pressure. The yellow residue was purified using column chromatography eluting with CH_2Cl_2 giving a yellow solid. Yield 90 mg (55 %). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67 (d, *J* = 2.0 Hz, 1H), 7.56 (s, 1H), 7.51 (d, *J* = 8.2 Hz, 2H), 7.45 – 7.39 (m, 2H), 7.24 (s, 1H), 7.22 (d, *J* = 8.4 Hz, 2H), 2.58 (d, *J* = 14.2 Hz, 2H), 2.23 (d, *J* = 13.2 Hz, 1H), 1.97 (td, *J* = 4.3, 13.2 Hz, 1H), 1.54 – 1.48 (m, 2H), 1.44 – 1.22 (m, 12H), 0.95 (t, *J* = 7.1 Hz, 6H), 0.87 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 176.2, 171.5, 149.5, 139.7, 137.8, 134.5, 133.3, 132.3, 131.8, 129.3, 128.6, 121.3, 121.2, 48.2, 46.6, 43.3, 43.2, 40.2, 37.8, 17.2, 17.1, 14.7, 14.5; HRMS (MALDI-FTMS: MH^+) calcd. for $C_{31}H_{36}N_4O_5S^+$ 577.2479, found 577.2474.

General procedure for coupling reaction of thioisocyanate **9a** or **9b** with adenosine-derived amine **10** or benzylamine **11**: Thioisocyanate **9a** or **9b** (1.0 equiv.) was treated with a solution of adenosine-derived amine **10** or benzylamine **11** (1.2 equiv.) in CH_2Cl_2 (8.0 mM) at -78 °C. After 24 h of stirring at -78 °C, the reaction mixture was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel, eluting with 20% acetone in chloroform to afford the thiourea.

Thiourea **9a**: ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.36 (s, 1H), 9.97 (s, 1H), 9.25 (s, 1H), 8.36 (s, 1H), 8.30 – 8.12 (m, 3H), 7.70 (d, J = 2.1, 8.4 Hz, 1H), 7.52 (d, J = 8.6 Hz, 2H), 7.44 (d, J = 8.4 Hz, 1H), 7.35 (s, 2H), 7.21 (d, J = 8.6 Hz, 2H), 6.20 (d, J = 2.6 Hz, 1H), 5.51 (dd, J = 2.6, 6.3 Hz, 1H), 5.09 (dd, J = 3.4, 6.3 Hz, 1H), 4.42 (td, J = 3.4, 6.9 Hz, 1H), 3.98 – 3.90 (m, 1H), 3.82 – 3.67 (m, 1H), 2.61 (d, J = 13.8 Hz, 2H), 2.02 (d, J = 12.6 Hz, 1H), 1.83 – 1.71 (m, 2H), 1.55 (s, 3H), 1.53 – 1.44 (m, 2H), 1.43 (s, 3H), 1.40 – 1.19 (m, 7H), 1.19 – 1.03 (m, 4H), 0.87 (t, J = 7.2 Hz, 6H), 0.79 (t, J = 7.3 Hz, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 180.9, 176.2, 172.1, 156.2, 152.8, 148.8, 148.3, 140.0, 139.5, 138.7, 131.7, 131.5, 129.7, 127.6, 126.0, 121.8, 119.2, 117.1, 113.5, 88.9, 83.7, 83.1, 81.7, 46.7, 45.7, 45.6, 42.2, 41.6, 40.1, 36.9, 27.0, 25.2, 16.5, 16.4, 14.7, 14.4; HRMS (MALDI-FTMS: MH^+) calcd. for $C_{44}H_{54}N_{10}O_8S^+$ 883.3919, found 883.3922.

Thiourea **9b**: ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.98 (s, 1H), 9.21 (s, 1H), 8.36 (s, 1H), 8.29 – 8.14 (m, 3H), 7.69 (d, J = 8.3 Hz, 1H), 7.58 (d, J = 8.6 Hz, 2H), 7.45 (d, J = 8.3 Hz, 1H), 7.35 (s, 2H), 7.21 (d, J = 8.6 Hz, 2H), 6.20 (d, J = 2.5 Hz, 1H), 5.50 (dd, J = 2.5, 6.2 Hz, 1H), 5.09 (dd, J = 3.2, 6.2 Hz, 1H), 4.42 (td, J = 3.2, 6.6 Hz, 1H), 3.98 – 3.90 (m, 1H), 3.80 – 3.71 (m, 1H), 2.63 (s, 3H), 2.61 (d, J = 14.0 Hz, 2H), 2.03 (d, J = 12.8 Hz, 1H), 1.91 – 1.74 (m, 2H), 1.55 (s, 3H), 1.53 – 1.46 (m, 2H), 1.41 – 1.27 (m, 7H), 1.34 (s, 3H), 1.14 – 1.08 (m, 4H), 0.87 (t, J = 7.1 Hz, 6H), 0.78 (t, J = 7.3 Hz, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 180.9, 176.2, 172.1, 156.2, 152.8, 148.8, 148.3, 140.0, 139.5, 138.7, 131.7, 131.5, 129.7, 127.6, 126.0, 121.8, 119.2, 117.1, 113.5, 88.9, 83.7, 83.1, 81.7, 46.7, 45.7, 45.6, 42.2, 41.6, 40.1, 36.9, 27.0, 25.2, 16.5, 16.4, 14.7, 14.4; HRMS (MALDI-FTMS: MH^+) calcd. for $C_{45}H_{56}N_{10}O_8S^+$ 897.4076, found 897.4073.

General procedure of competition studies in the presence of additive for coupling reaction of adenosine derived amine **10** or **11** with thioisocyanate **9a** and **9b**:

Method A: Adenosine derived amine **10** (8.0 mM) or benzylamine **11** (8.0 mM) in CH_2Cl_2 was added very slowly to a solution of thioisocyanate **9a** and **9b** (8.0 mM), and additive **5a** in CH_2Cl_2 at -78 °C. After 24 h of stirring at -78 °C, the mixture was analyzed by HPLC using the peak areas [254 nm].

Method B: Thioisocyanate **9a** or **9b** (8.0 mM) was added very slowly to a solution of amino adenosine **10** (8.0 mM), and benzylamine **11** (8.0 mM), and thiourea **5a** (0.00 equiv, 0.25 equiv, 0.50 equiv) in CH_2Cl_2 at -78 °C. After 24 h of stirring at -78 °C, the mixture was analyzed by HPLC using the peak areas [254 nm].

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