

Four acid-catalysed dehydration reactions proceed without interference†

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Four acid-catalysed dehydration reactions can proceed in one pot, simultaneously and without interference, to yield one imine, one acetal (or boronic ester), one ester and one alkene, even though many other cross-products could be conceived. This advanced self-sorting behaviour is attributed to different dehydration rates, brought about by dissimilar electronic properties of starting materials.

An ability to synthesize multiple well-defined products from complex (“messy”) mixtures of starting materials is one of the hallmarks of living systems. In fact, at the origin of life, it is likely that selective reactions needed to occur within complex chemical mixtures that did not yet have highly specific enzyme catalysts.¹ Parallel synthesis could also yield tremendous benefits to the chemical industry if multiple value-added products could be produced simultaneously in a single reactor. Despite these practical and fundamental benefits, little work has been devoted to the study of multiple reactions occurring within the same laboratory flask. Otera’s group has been active in the area of “shotgun” processes,² wherein two reactions occur at rates sufficiently different to allow them to proceed in a single flask without interference. This principle was exemplified by the parallel operation of aldehyde allylation and aldol reaction,^{2a} multiple Diels–Alder reactions,^{2b} and in the one-pot combination of Diels–Alder reaction, alcohol acetylation and aldehyde allylation.^{2c} It was also applied in total syntheses of small natural products.^{2d,e} The same group has also demonstrated parallel recognition:³ non-interfering parallel reactions which occur at sites that react completely independently from each other.

In the domain of dynamic combinatorial chemistry,⁴ multiple non-interfering metal–ligand binding events have been utilized by Nitschke⁵ and Schmittel,⁶ among others. In a seminal paper, Isaacs⁷ has shown that eight hydrogen-bonding ensembles maintain their

partner association preferences even when they are all placed in a single solution.

We have recently shown that libraries of as many as 25 equilibrating members can self-sort⁸ into a handful of pure products through iterative application of an irreversible chemical⁹ or physical¹⁰ stimulus. In this contribution, we examine the question of whether similar reduction of complexity is possible in a system where chemical functionalities of reacting species are different and multiple reactions are involved.

As the model system, we chose a set of five reactions, all of which are catalysed by Brønsted acids: (1) imine formation from aldehydes and primary aromatic amines; (2) acetalization of aldehydes and alcohols; (3) boronic ester formation from alcohols and boronic acids; (4) esterification of carboxylic acids with alcohols; and (5) alkene formation through intramolecular dehydration of alcohols. All of these reactions are in principle reversible, but equilibria can be forced toward the dehydrated products by H₂O removal *via* a Dean–Stark trap. In addition, compounds like aldehydes, alcohols, and diols can engage in reactions with multiple partners (*e.g.* an alcohol can form an ester with a carboxylic acid, a boronic ester with a boronic acid, an acetal with an aldehyde or an alkene). This fact allowed the exploration of situations wherein multiple species can compete for a reaction partner. We examined the behaviour of various libraries of starting materials chosen from Fig. 1.

Three sets of reactions were performed. In the first set (Scheme 1: top left and entries #1 and 2 in the table), we combined equimolar amounts (0.32 mmol) of aldehyde **1a**, boronic acid **5a** or **5b**,¹¹ aniline **2a**, diol **6a**, carboxylic acid **3a** and alcohol **4c**, along with a threefold excess of alcohol **4a** (0.96 mmol).¹² A catalytic amount of *p*-toluenesulfonic acid was added and the solution was heated at reflux for 2 d with H₂O removal. Within such a library of starting materials, many possible products could have formed: one imine, four acetals, four boronic esters, four esters and two alkenes, and possibly other dehydration products (*e.g.* amides or boroxines). However, only four discrete products were observed, corresponding to the reactions highlighted by thick red lines in Scheme 1, top left.

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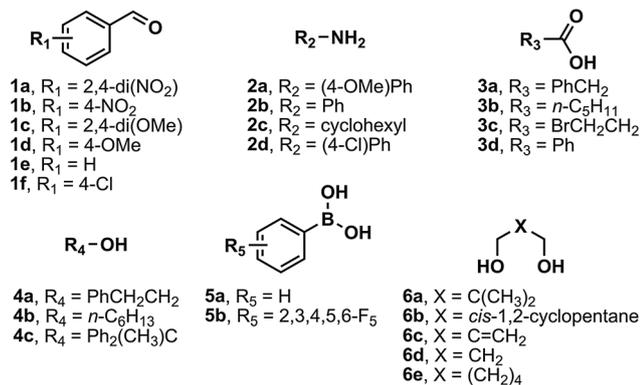


Fig. 1 Compounds examined in this study.

The top table in Scheme 1 details this selectivity: one amine (from **1a** and **2a**, pathway A), one boronic ester (from **5a/5b** and **6a**, pathway B), one ester (from **3a** and **4a**, pathway C) and one alkene (from **4c**, pathway D) were formed, in yields that typically exceeded 90% as determined by ¹H NMR spectroscopy with an internal standard.

In the second set of thirteen experiments (Scheme 1: top centre and entries #3–15), boronic acid was replaced by a second aldehyde, setting up a competition between the two aldehydes—as each could form either an imine or an acetal, or both. In total, at least 16 products could be formed: two imines, eight acetals, four esters and four alkenes. In the benchmark reaction (entry #3), electron-poor aldehyde **1a** reacted with amine **2a** to form an imine (pathway A, 84%) and with **6a** to give a miniscule amount of acetal (pathway E, 0.4%). Electron-rich **1c** was dominantly converted into an acetal with **6a** (pathway B, 77%),

Entry	Aldehyde	Boronic Acid	Amine	Diol	Alcohol #1	Alcohol #2	Carboxylic Acid	A	B	C	D			
1	1a	5a	2a	6a	4a	4c	3a	93	99	99	98			
2	1a	5b	2a	6a	4a	4c	3a	97	74	99	99			
	Aldehyde #1	Aldehyde #2	Amine	Diol	Alcohol #1	Alcohol #2	Carboxylic Acid	A	B	C	D	E	F	
3	1a	1c	2a	6a	4a	4c	3a	84	77	96	99	0.4	9	
4	1a	1e	2a	6a	4a	4c	3a	92	79	98	99	1	5	
5	1b	1d	2a	6a	4a	4c	3a	75	72	59	99	—	5	
6	1b	1f	2a	6a	4a	4c	3a	52	52	99	99	48	43	
7	1a	1c	2b	6a	4a	4c	3a	86	80	98	99	—	—	
8	1a	1c	2c	6a	4a	4c	3a	72	95	43	99	—	—	
9	1a	1c	2d	6a	4a	4c	3a	83	74	99	99	—	—	
10	1a	1d	2a	6b	4a	4c	3a	98	94*	99	99	—	1	
11	1a	1d	2a	6c	4a	4c	3a	86	64	93	99	—	1	
12	1a	1c	2a	6d	4a	4c	3a	96	92	91	99	—	4	
13	1a	1c	2a	6a	4b	4c	3b	79	76	75	99	1	12	
14	1a	1c	2a	6a	4a	4c	3c	85	84	99	99	4	13	
15	1a	1c	2a	6a	4a	4c	3d	90	78	11	98	1	10	
	Aldehyde #1	Aldehyde #2	Amine	Diol #1	Diol #2	Alcohol	Carboxylic Acid	A	B	C	D	F	G	H
16	1a	1e	2a	6a	6d	4c	3a	98	54	95	98	—	5	46
17	1a	1c	2a	6a	6e	4c	3a	78	77	99**	99	5	—	—

* As a mixture of two diastereomers.

** As a mixture of monoester and diester, with overlapping NMR signals.

Scheme 1 Self-sorting of complex reaction mixtures during acid-catalysed dehydrations. Dominant reaction pathways are highlighted with thick red lines, minor pathways with full black lines. Pathways that were not observed but were theoretically possible are shown in dashed black lines.

but a minor imine product (with **2a**, pathway F, 9%) was also observed. As in the previous set of experiments, carboxylic acid **3a** and alcohol **4a** formed an ester (pathway C, 96%) and alcohol **4c** exclusively dehydrated into an alkene (pathway D, 99%).

We subsequently probed the effect of replacing individual components of this self-sorting system. Aldehydes can be switched without erosion of selectivity (entries #4 and 5), but once they become too close in their electronic properties (entry #6, where both **1b** and **1f** are electron-poor), imines and acetals are formed indiscriminately. Switching the primary amine (entries #7–9) does not lower self-sorting selectivity. With alkylamine **2c**, esterification of **3a** with **4a** proceeds in only 43% yield, which can be rationalized by the formation of small amounts of amide between **2c** and **3a** (as well as other unidentified products). As entries #10–12 show, diol can also be varied rather freely, although **6c** (entry #11) shows a lower yield, presumably on account of the Thorpe–Ingold effect. Switching the carboxylic acid (entries #14 and 15) and carboxylic acid along with alcohol (entry #13) still keeps the selectivity largely unaffected, although esterification of benzoic acid (**3d**, entry #15) proceeded only to 11% conversion.¹³

This high preference for the dominant products observed in experiments #3–5 and #7–15 can tentatively be explained as follows (entry #3 will be used as an example). Donor–acceptor imines are both more stable and formed faster than their donor–donor counterparts. Therefore, the electron-poor **1a** reacts quickly with amine **2a**, forcing aldehyde **1c** into an acetal with diol **6a**—which is entropically favoured relative to acetals formed from **1c** and two molecules of a monool. Unimolecular dehydration of tertiary alcohol **4c** into an alkene is quick,¹⁴ leaving **4a** with no choice but to slowly (in a bimolecular reaction) form an ester with **3a**. Curiously, excess of **4a** still does not compete in acetal formation: it is observed to be unchanged at the end of the reaction.

The final set of experiments (Scheme 1: top right and entries #16 and 17) examined what happens when one of the monools is replaced with a diol—thus setting up a competition between two aldehydes and two diols. Thirteen products: two imines, four acetals, five esters, and two alkenes could be expected. Intriguingly, in neither of the two experiments, electron-poor aldehyde **1a** formed an acetal—even though it was offered a choice of diols (therefore, pathway E is omitted from the last table in Scheme 1). In the first experiment (entry #16), two diols (**6a** and **6d**) were of the same length and aldehyde **1c** could not distinguish them (pathway B: 54%, pathway H: 46%). Carboxylic acid then reacted with the excess of **6d** to produce an ester (pathway C, 95%). The second experiment replaced **6d** with longer **6e**, restoring the original selectivity: only four products from pathways A–D were observed.

Observed reaction preferences appear to be kinetic in character. By focusing on reaction #3 in Scheme 1 and observing its progress by ¹H NMR spectroscopy, we were able to estimate rates of formation of dehydrated products following the trend: alkene ≈ imine > acetal > ester. We then independently prepared the crossover imine and acetal species not observed in the actual reaction: imine formed from **1c** and **2a** and acetal from **1a** and **6a**. When these two “wrong” products were heated in *anhydrous* PhMe

at reflux (to simulate the conditions at the end of self-sorting reactions) in the presence of *p*-toluenesulfonic acid, no equilibration was observed even after 4 d—suggesting that the mixture composition more likely corresponds to kinetic distribution of the products. No equilibration was observed in a similar experiment where “wrong” ester and acetal partners were heated for 2 d in the presence of an acid catalyst.¹⁵

In conclusion, we have demonstrated that dehydration reactions yielding imine, acetal/boronate ester, ester and alkene products may be accomplished in one-pot with a common—and very simple—acid catalyst. A single set of dehydrated products stems from different mechanisms for the participant reactions and electronic properties of starting materials, which together translate into sufficiently different rates of competing reactions. The system is modular, but within limits. While individual components can be swapped, examples of aldehydes with similar electronic properties and diols of similar chain lengths showed that selectivity quickly erodes when substrates are offered a “confusing” choice of reagents. Future work will focus on applications of this process, including testing whether similar parallel reactions occur in mixtures containing activated amino acid derivatives, to establish whether privileged oligopeptide structures could form in the absence of enzymatic catalysis.

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Notes and references

- Origin of Life: Chemical Approach*, ed. P. Herdewin and M. V. Kisakürek, Wiley-VCH, Weinheim, 2008.
- (a) Y. Nagano, A. Orita and J. Otera, *Bull. Chem. Soc. Jpn.*, 2003, **76**, 2183–2189; (b) Y. Nagano, A. Orita and J. Otera, *Tetrahedron*, 2002, **58**, 8211–8217; (c) A. Orita, Y. Nagano, K. Nakazawa and J. Otera, *Synlett*, 2000, 599–602; (d) Y. Nagano, A. Orita and J. Otera, *Synlett*, 2003, 684–688; (e) Y. Nagano, A. Orita and J. Otera, *Tetrahedron*, 2003, **59**, 5569–5578.
- (a) J. Chen and J. Otera, *Angew. Chem., Int. Ed.*, 1998, **37**, 91–93; (b) J. Chen, K. Sakamoto, A. Orita and J. Otera, *Tetrahedron*, 1998, **54**, 8411–8420.
- (a) J. N. H. Reek and S. Otto, *Dynamic Combinatorial Chemistry*, Wiley-VCH, Weinheim, 2010; (b) P. T. Corbett, J. Leclair, L. Vial, K. R. West, J.-L. Wietor, J. K. M. Sanders and S. Otto, *Chem. Rev.*, 2006, **106**, 3652–3711.
- (a) A. G. Salles Jr., S. Zarra, R. M. Turner and J. R. Nitschke, *J. Am. Chem. Soc.*, 2013, **135**, 19143–19146; (b) M. Hutin, C. J. Cramer, L. Gagliardi, A. R. M. Shahi, G. Bernardinelli, R. Cerny and J. R. Nitschke, *J. Am. Chem. Soc.*, 2007, **129**, 8774–8780.
- (a) M. L. Saha and M. Schmittel, *J. Am. Chem. Soc.*, 2013, **135**, 17743–17746; (b) M. L. Saha, J. W. Bats and M. Schmittel, *Org. Biomol. Chem.*, 2013, **11**, 5592–5595; (c) K. Mahata, M. L. Saha and M. Schmittel, *J. Am. Chem. Soc.*, 2010, **132**, 15933–15935.
- A. Wu and L. Isaacs, *J. Am. Chem. Soc.*, 2003, **125**, 4831–4835.
- (a) Q. Ji, R. C. Lirag and O. Š. Miljanić, *Chem. Soc. Rev.*, 2014, **43**, 1873–1884; (b) M. M. Safont-Sempere, G. Fernandez and F. Würthner, *Chem. Rev.*, 2011, **111**, 5784–5814; (c) K. Osowska and O. Š. Miljanić, *Synlett*, 2011, 1643–1648.
- K. Osowska and O. Š. Miljanić, *J. Am. Chem. Soc.*, 2011, **133**, 724–727.
- (a) Q. Ji, N. El-Hamdi and O. Š. Miljanić, *J. Chem. Educ.*, 2014, **91**, 830–833; (b) Q. Ji and O. Š. Miljanić, *J. Org. Chem.*, 2013, **78**, 12710–12716; (c) R. C. Lirag, K. Osowska and O. Š. Miljanić, *Org. Biomol. Chem.*, 2012, **10**, 4847–4850; (d) K. Osowska and O. Š. Miljanić, *Angew. Chem., Int. Ed.*, 2011, **50**, 8345–8349.
- Formation of imines and boronate esters has been shown to occur orthogonally, and has been used in the synthesis of cage compounds.

- See, for example: (a) B. İçli, N. Christinat, J. Tönnemann, C. Schüttler, R. Scopelliti and K. Severin, *J. Am. Chem. Soc.*, 2009, **131**, 3154–3155; (b) N. Christinat, R. Scopelliti and K. Severin, *Angew. Chem., Int. Ed.*, 2008, **47**, 1848–1852.
- 12 Alcohol was always added in excess (3 eq. compared to other starting materials) to ensure complete consumption of carboxylic acid and to remain available to compete with diol for acetal formation.
- 13 (a) A. S.-Y. Lee, H.-C. Yang and F.-Y. Su, *Tetrahedron Lett.*, 2001, **42**, 301–303; (b) M.-Y. Chen and A. S.-Y. Lee, *J. Chin. Chem. Soc.*, 2003, **50**, 103–108.
- 14 A carboxylic acid can add to the alkene formed by the dehydration of the tertiary alcohol (see: J. Otera and J. Nishikido, *Esterification. Methods, Reactions, and Applications*, Wiley-VCH, Weinheim, 2nd edn, 2010, p. 10), but we did not observe this process in the examined reactions. A secondary alcohol (1,2-diphenylethanol) was also used in place of **4c**: while ¹H NMR analysis showed no ester formation, dehydration of the secondary alcohol did not go to completion after several days at reflux, reaching a maximum conversion of 32%.
- 15 If either an acetal or the ester bore a free –OH group (e.g. in a monoester of **6d** and **3a**), equilibration did proceed.