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Insights into the spontaneous emergence of enantioselectivity in an asymmetric Mannich reaction carried out without external catalyst

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ABSTRACT

ESI-MS, chiral HPLC, time-resolved ^{1}H NMR and optical rotation measurements were performed to gain insights into the nature of spontaneous mirror symmetry breaking in the catalyst-free Mannich reaction of PMP protected α-iminoethylglyoxylate with hydroxyacetone. Spontaneous temporary generation of enantiomeric excesses of up to 7.4% in the major *syn* diastereomer is reproducibly observed in aqueous phosphate buffers, starting from achiral conditions. The *syn*-product ee values for both enantiomers [(2*S*,3*S*) and (2*R*,3*R*)], although not with stochastic distribution, have been observed with no clear preference for either enantiomer.

1. Introduction

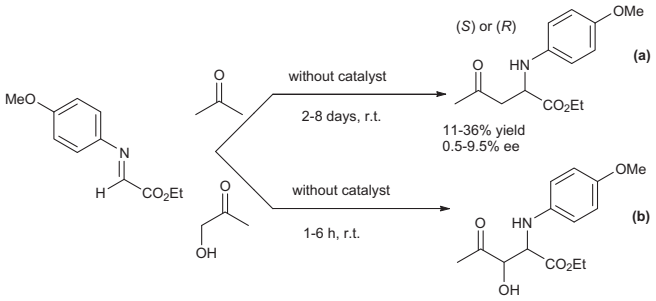
The origin of biomolecular homochirality, that is that only one enantiomeric form of amino acids dominates in Nature, still belongs to one of the most profound conundrums in science.[1–8] Could the (*R*)/(*S*) symmetry of biomolecules have become broken spontaneously? One of the main dogmas of asymmetric synthesis has it that enantioselective reactions always give racemic products in the absence of chiral inductors such as chiral catalysts, auxiliaries, solvents or circularly polarized light.[9–11] This partly explains the sensation caused by Soai's report in 1995 on the dramatic spontaneous asymmetric amplification in the irreversible alkylation reaction of pyrimidine carbaldehydes with diisopropyl zinc.[12] At completion, the reaction produces a dominance of either the (*R*)- or (*S*)-product in the reaction mixture, depending on an initial accidental and miniscule enantiomeric imbalance. It has been disclosed that autocatalytically active homochiral dimers of the product seem to be mainly responsible for the symmetry breaking effect.[13–16]

The possibility of spontaneous autoamplification of ee in chemical reactions has already been the focus of several theoretical investigations.[17–25] The first proposal of a mathematical mechanism for the spontaneous emergence of enantiomeric excess through enantioselective autocatalysis in conjunction with mutual inhibition of enantiomers was made by Charles Frank in 1953.[26] Symmetry breaking by spontaneous deracemisation of chiral conglomerates has also been reported.[27–29]

In this process, autocatalysis was again proposed to be involved in the crystallization.[30] Very recently, the spontaneous generation of a chiral surplus was implied in the theoretical study of the product assisted hemiacetal formation of acetone with trihaloacetaldehydes.[31]

Self-replication processes of products have been studied earlier, involving oligomeric nucleotide molecules and β-sheet peptides.[32,33] Even before the Soai reaction was discovered, it was suggested that an enantioselective autocatalytic reaction in conjunction with a positive non-linear effect of catalyst versus product ee should lead to spontaneous asymmetric amplification.[34]

In 2007, it was reported that in the product assisted asymmetric Mannich reaction[35] of PMP protected α-iminoethylglyoxylate with acetone, a spontaneously generated product enantiomeric excess of 9.4% can be observed with 31% yield after four days reaction time – even when the initial reaction mixture is achiral or racemic (Scheme 1a).[36] This result has indicated that seemingly well-known[37] organic reactions might have much more complicated mechanisms than was previously assumed. In order to study this process further, we decided to use hydroxyacetone as the donor



Scheme 1. Mannich reactions in the absence of external catalyst.

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(Scheme 1b), instead of acetone, because of the higher reactivity of the former, and hence, the expectation of reduced reaction times.

Herein we report our results on the reaction kinetics of this transformation using ^{1}H NMR studies, which show an induction period of product formation thus evidencing the involvement of an autoinductive process. Based on ESI-MS measurements and ^{1}H NMR studies, we propose the in situ formation of an organic base, a diamine side product, which could assist in the enolate formation from the ketone. Furthermore, polarimetry was used to monitor the variation of the optical rotations during the reaction. It is also shown that optical rotation emerges spontaneously and temporarily at the beginning of the reaction.

2. Results and discussion

Firstly, the reaction of PMP protected α-iminoethylglyoxylate with hydroxyacetone (Scheme 1b)[37] was studied under various conditions (solvent, temperature, reactant concentration) and without any external catalyst. The results are summarized in Table 1. The diastereoselectivity is almost the same (84:16 to 89:11 dr, entries 1–14) under most of the studied conditions and for the investigated reaction times, except for the results in aqueous conditions (in phosphate buffer) measured after 1 h reaction time (66:34 to 72:28 dr, entries 15–18), with the *syn*-diastereomer always being predominant. This implies that the *syn*-isomer is the thermodynamically more stable one. The yield strongly depends on the temperature; the higher temperatures gave better yields after the same reaction time: while in DCM at room temperature after 1 h, the yield was only 9.4% (Table 1, entry 1), it is 28.4% at 40°C (entry 10).

Table 1
Mannich reaction of imine with hydroxyacetone (from Scheme 1b) carried out without an external catalyst

Entry	Time, h	Solvent	*T*, °C	Yield[a] (%)	dr[b] (*syn*:*anti*)	ee[b] (%) (*syn*)
1[c]	1	DCM	rt	9.4	88:12	*rac*
2[d]	1	DCM	rt	n.d.	86:14	1.0 (2*S*,3*S*)
3[c]	1	DCM	0	n.d.	82:18	*rac*
4[d]	1	DCM	0	n.d.	89:11	*rac*
5[d]	1	DCM	0	n.d.	84:16	2.1 (2*S*,3*S*)
6[c]	3	DCM	0	n.d.	88:12	*rac*
7[d]	6	DCM	0	n.d.	84:16	2.0 (2*S*,3*S*)
8[e]	6	DCM	0	15.2	88:12	2.4 (2*R*,3*R*)
9[c]	4	DCM	−20	10.3	86:14	*rac*
10[c]	1	DCM	40	28.4	82:18	*rac*
11[c]	6	THF	rt	14.7	86:14	4.3 (2*R*,3*R*)
12[c]	6	THF	0	15.7	86:14	1.6 (2*S*,3*S*)
13[d]	3	THF	0	n.d.	82:18	*rac*
14[c]	6	Buffer[f]	rt	15.3	86:14	1.4 (2*R*,3*R*)
15[d]	1.7	Buffer[f]	rt	n.d.	66:34	4.4 (2*S*,3*S*)
16[d]	1	Buffer[f]	rt	n.d.	70:30	6.3 (2*R*,3*R*)
17[d]	1	Buffer[f]	rt	n.d.	72:28	7.4 (2*S*,3*S*)
18[d]	1	Buffer[f]	rt	n.d.	67:33	5.1 (2*S*,3*S*)

[a] Yields of the isolated products.
[b] Determined by chiral HPLC analysis (Daicel Chiralpak IA) in comparison with authentic racemic material.
[c] 0.3 M imine concentration.
[d] 0.5 M imine concentration.
[e] 0.1 M imine concentration.
[f] Phosphate buffer at pH 7.

When the reaction was left to run in a buffer solution for 6 h, instead of one, the dr and yield approach the values observed for the reactions in organic solvents (entry 14).

Despite the achiral starting conditions, small enantiomeric excess values of up to 7.4% have reproducibly been observed in the *syn*-product from one to a few hours after the start of the reaction in some experiments in accordance with similar results for the reaction of acetone with the same imine, as reported previously.[36] Notably, we observed *syn*-product ee values for both enantiomers [(2*S*,3*S*) and (2*R*,3*R*)], although not with stochastic distribution. No clear preference for either enantiomer can be recognized. It should be noted that the initial conditions differ in the experiments and that the small number of runs forbids a statistical evaluation. Several reaction mixtures remain exactly racemic when the ee is measured even after only 1 h (entries 1, 3, 4 and 10) and after up to 4 h (entries 6, 9 and 13). After two days reaction time, all mixtures were fully racemic as could be predicted from equilibrium thermodynamics.

Monitoring of ee values in two independent experiments in a phosphate buffer at pH 7 (entries 15 and 16) in short intervals, revealed that in both cases, the ee value observed in the first measurement decreased rapidly to a near-zero value after about 1.5 h (Fig. 1). This shows that thermodynamic equilibrium is approached quickly. Significant deviations from the equilibrium values occur shortly after the reaction starts at low yields (Table 1).

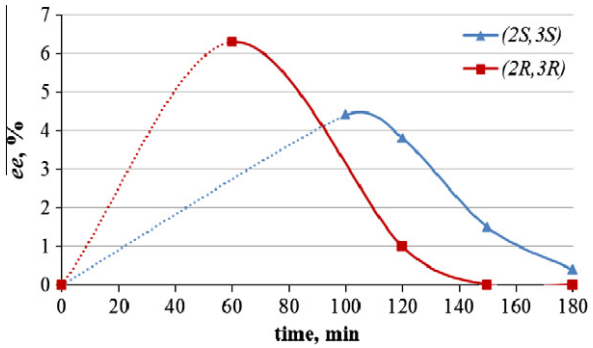

Figure 1. Monitoring of the ee-values with the reaction time under aqueous conditions (phosphate buffer) for the *syn*-product. (Table 1, entries 15 and 16).

We also studied the time dependence of the imine conversion in $CDCl_3$, employing ^{1}H NMR (Fig. 2). After 80 min, that is at about the time when ee values begin to decrease in the phosphate buffer (Fig. 1), the imine was fully consumed. We observed an *S*-shaped curve with an induction period and significant rate of acceleration, which indicates the involvement of an autoinductive process.

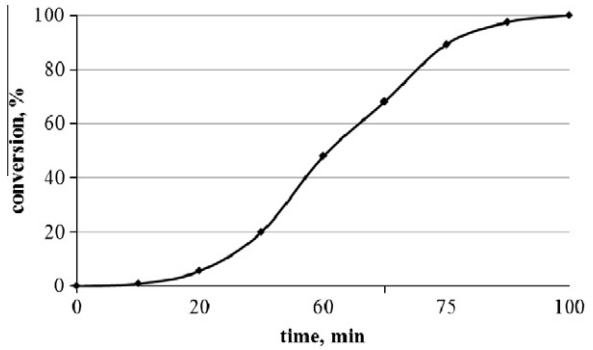

Figure 2. Conversion time profile for the Mannich reaction carried out with imine (c = 0.5 M) and hydroxyacetone (3 equiv) in $CDCl_3$.

In order to verify the spontaneous emergence of the enantiomeric excess in the Mannich reaction, we carried out optical rotation measurements with a polarimeter in DCM (Fig. 3). In four consecutive independent experiments under the same conditions we observed significant optical rotation values increasing shortly

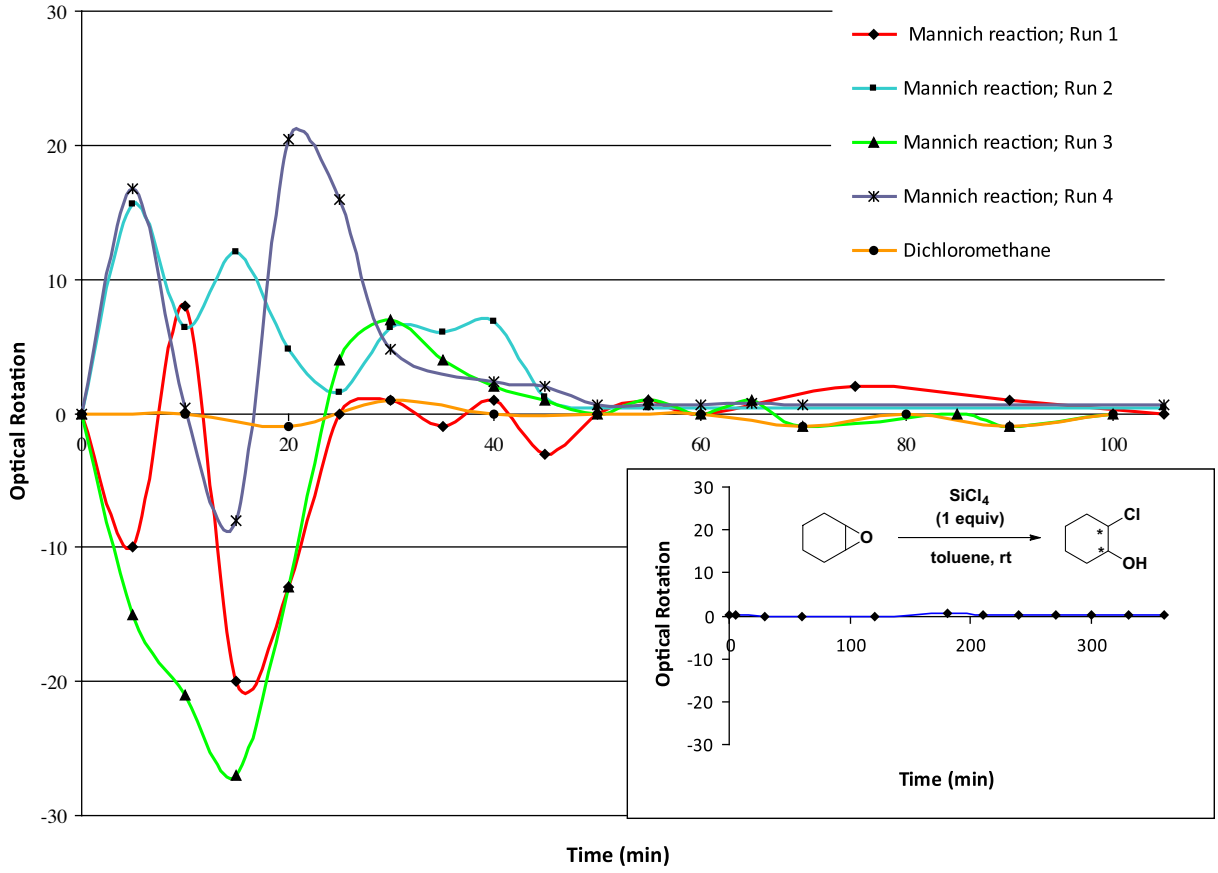

Figure 3. Monitoring of the optical rotation during the reaction of imine (c = 0.5 M) with hydroxyacetone (10 equiv) in DCM (4 independent runs).

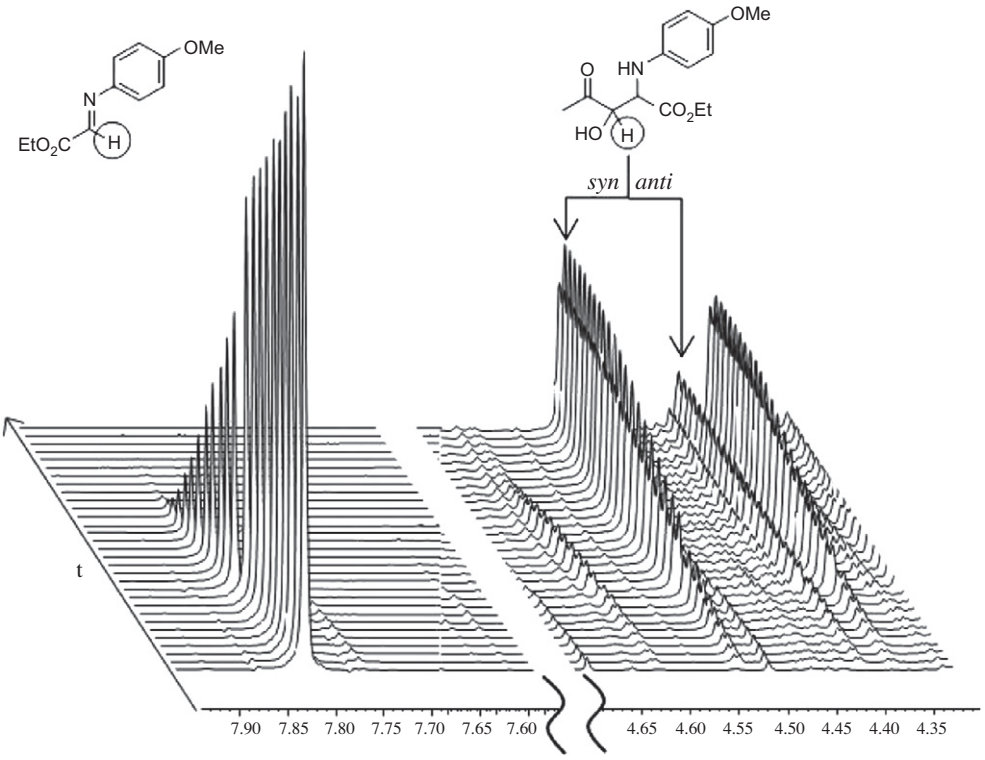

Figure 4. Fragments of time-resolved ^{1}H NMR spectrum (400 MHz) recorded during the reaction of imine (c = 0.5 M) with hydroxyacetone (3 equiv) in $CDCl_3$.

after mixing the reactants. The rotation angle vividly swerves from positive to negative values or vice versa during the first 40 min of the reaction. A control experiment with pure solvent (DCM) remained near the zero line throughout the whole observation time. To determine whether the effect depends on the nature of the reaction, we also performed a similar monitoring experiment with the irreversible meso epoxide ring opening reaction shown in the insert in Figure 3: the optical rotation was negligible during the whole reaction time. This shows that not all stereoselective reactions display the effect of spontaneous mirror symmetry breaking. The epoxide ring opening differs from the Mannich reaction in its irreversibility, which might indicate that reversibility is crucial for the observation of the aforementioned effect. Furthermore, the product of the epoxide ring opening (2-chlorocyclohexanol) could hardly compete with the external promoter/reagent $SiCl_4$ (Lewis acid) in activating the epoxide. Hence, product assistance is unlikely in this reaction.

These observations motivated us to further elucidate the mechanism of the Mannich reaction with time-resolved ^{1}H NMR (Fig. 4). We were able to detect the formation of several unidentified species in the course of the reaction (see also SI). Some of the species appear to be intermediates (e.g. see signal at 4.6 ppm, which almost disappears during the later stages of the observation time window). We suspect that some of the species might be side products taking part in the Mannich reaction.

Since the observation time of the highest ee values at about 1 h after the beginning of the reaction approximately coincides with the time after which complete conversion of the imine was achieved, we suspected that the imine conversion might provide the thermodynamic driving force fueling the non-equilibrium process necessary to deviate from the racemic state.

To gain an indication of the potential nature of these side products, we performed ESI-MS measurements for the reaction of hydroxyacetone with imine, and also, for the previously studied reaction of acetone with the same imine. In both cases we observed (besides other peaks, which correspond, to the imine and product) the formation of a species at m/z 352.2 (Fig. 5), from which it is obvious that the ketone (acetone or hydroxyacetone) is not involved in the formation of this species. In both reactions, we observed the formation of anisidine traces (characteristic signal at m/z 124.1 $[M+H]^+$ in ESI-MS or LC–MS spectra).

Therefore, we hypothesized that the peak at m/z 352.2 might correspond to the presumed diamine product formed in the reaction of the imine with anisidine. To determine if our hypothesis was plausible, we stirred the 1:1 mixture of the imine with anisidine and measured ^{1}H NMR and ESI-MS spectra at different time intervals. A peak at m/z 352.2 (corresponding to the anticipated species) was detected in ESI-MS spectra recorded after 3 h and characteristic signals of the formed product in ^{1}H NMR spectra, measured after 10 and 60 min, respectively (see SI). Injection of a sample taken from the above reaction mixture into a chiral HPLC column, which we employed in the stereoselectivity determinations (Table 1), showed that the diamine had the same retention time as the (2*R*,3*S*)-enantiomer of the *anti*-diastereomer

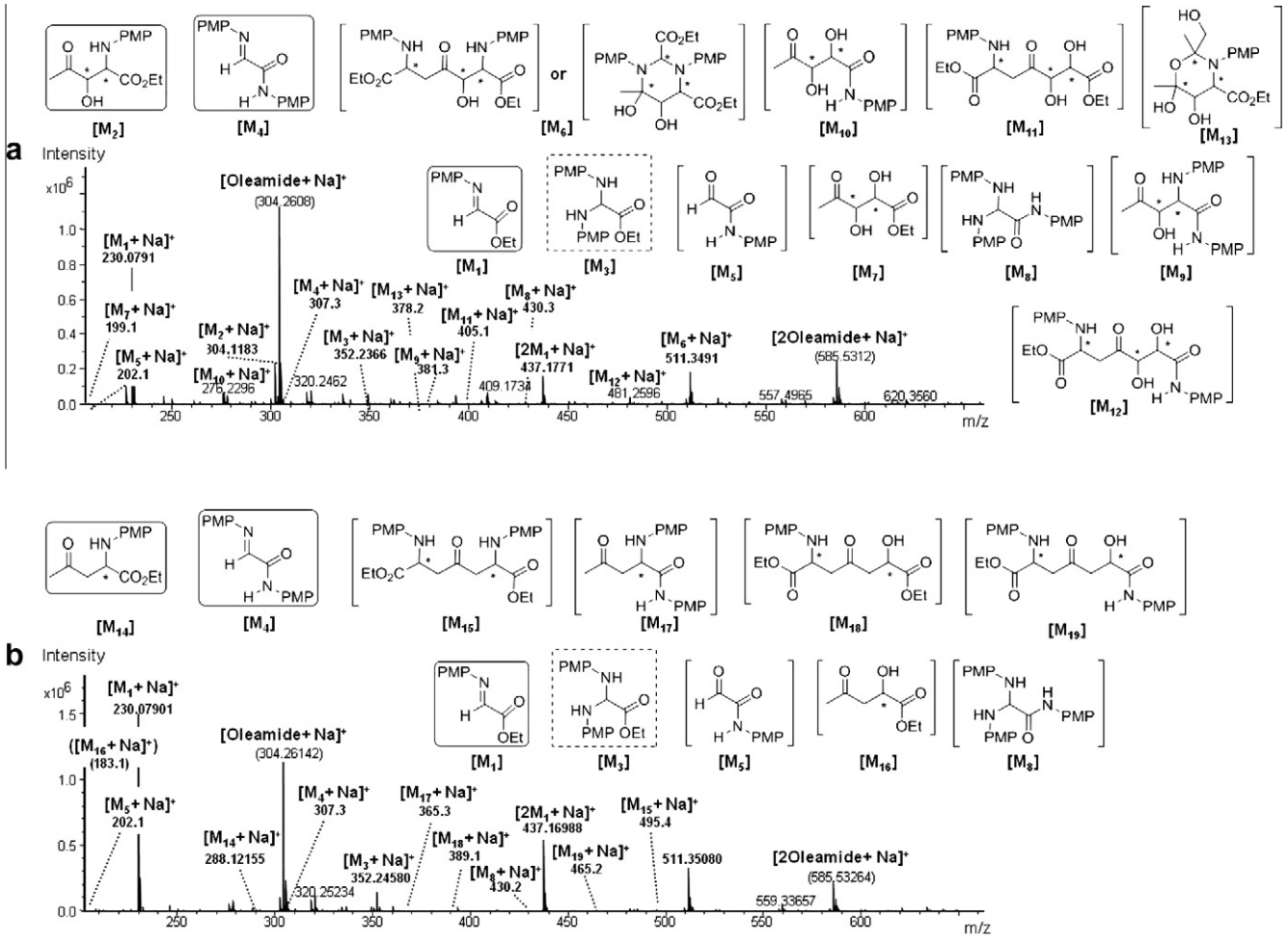

Figure 5. ESI-MS spectra (positive mode) for the reactions of (a) hydroxyacetone with imine (60 min after the start of the reaction); and (b) acetone with imine (21 h after the reaction start).

(see SI). This means that the ee values in the minor *anti*-diastereomer are not reliable due to peak overlapping and have therefore not been reported in Table 1. This might also explain the lower diastereomeric ratio (ca. 70:30 *syn*/*anti*) observed after 1 h in phosphate buffer (entries 15–18, Table 1).

Notably, the same side product observed in the reaction of the imine with acetone has a pronouncedly different retention time than either the (*R*)- or (*S*)-product (see SI).

The information thus gained led us to assume the following proposal for the involvement of the formed base (side product) in the Mannich reaction, relevant for both transformations with acetone and hydroxyacetone respectively: *via* a reversible equilibrium, the imine can revert to its constituents, anisidine and ethylglyoxylate, followed by the reaction of imine with the formed anisidine to give the side product (a diamine species), which we assume will act as an in situ formed organocatalyst and which might assist in the formation of an enolate as a more active nucleophile, thus promoting the first step of the Mannich reaction. This first step is apparently rate determining, which could explain the conversion time profile shown in Figure 2. The second step, the CC bond formation, is configuration determining and could potentially be affected by the involvement of the chiral Mannich product or by a chiral side product, which might direct the product formation in an enantioselective manner. Such product assistance through activation by hydrogen bridging in the configuration determining step of the Mannich reaction has been previously reported.[35] It should be noted that this asymmetric 'organoautocatalysis', while affecting the product ee value, does not necessarily result in reaction rate acceleration. This mechanistic hypothesis, however, does not explain why ee values can emerge spontaneously.

As proposed earlier,[35a,36] the *syn*-product assisted nucleophilic addition implies the initial formation of hydrogen bonded product homo- (*RR*·*RR* or *SS*·*SS*) and heterodimer (*RR*·*SS*) complexes. When the reaction is enantioselective, homodimers must form faster than heterodimers. The homodimers may be higher in energy with respect to heterodimers and therefore may dissociate faster to the monomeric chiral autocatalysts which could became engaged again in further catalytic cycles, while the heterodimers could have a much slower lifecycle.[38] However, first order enantioselective 'autocatalysis' alone cannot give rise to asymmetric amplification.[13]

A further assumption is necessary. Due to a fluctuation, one of the two homodimers may form accidentally with a tiny excess. This small deviation can be amplified, as monomeric product enantiomers (released through dissociation of the initially formed dimeric products) may recombine again fast to more stable heterodimers (before becoming engaged again in a further round of enantioselective autocatalysis), resulting in the depletion of the minor enantiomer. This is reminiscent of the well-known mutual inhibition mechanism of Frank, where the initial opposite enantiomer products of the enantioselective autocatalysis step recombine rapidly to irreversibly give a heterodimer, thereby being removed from the reaction.[26] Such a combination of an autocatalytic reaction step of only linear order in the product concentration and mutual inhibition allows spontaneous autoamplification of the

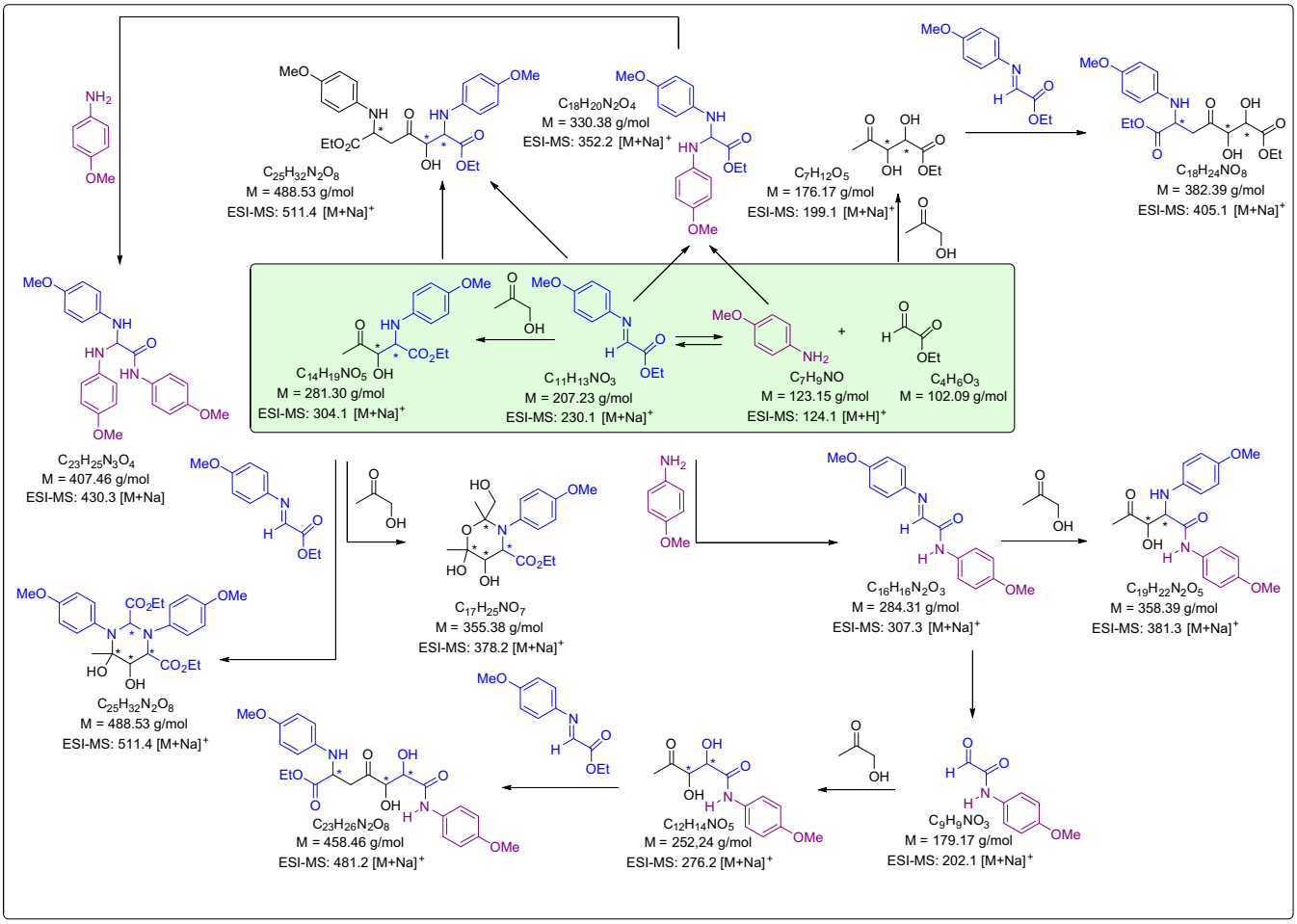

Figure 6. Proposed network of the Mannich reaction system.

ee, even when the heterodimer formation is not irreversible.[20,31] In this case, the maximum achievable and spontaneously generated overall ee value (taking into account the product molecules bound in the form of heterodimers) would obviously be small, probably only a few percent just as we observe here.

The ee values, once generated, soon fall back to their zero equilibrium values (Fig. 1); this is indicative of the reversibility of the whole process. Unfortunately, and in contrast to the famous second order autocatalytic Soai reaction,[13,16] the rate determining and configuration determining reaction steps most likely do not coincide for the Mannich reaction studied herein. As a consequence, the background reaction (without product assistance), which gives a racemic product, and the potentially product assisted reaction pathway, both possess the same activation barrier. This lowers the temporarily observable enantiomeric excess further. It remains to find examples in which the background reaction is suppressed.

To obtain spontaneously even larger ee values closer to enantiomeric purity, it is necessary to postulate a pathway for recycling the minor enantiomer back to the reactant.[36,39] Such a hypothetical process can, however, only take place under explicit non-equilibrium conditions in order to avoid a violation of microscopic reversibility.

The whole reaction network is definitely complex. A conjecture on its nature is shown in Figure 6.

3. Conclusion

In conclusion, we have gained further insights into an asymmetric Mannich reaction, carried out without external catalyst, and which is capable of generating small ee values spontaneously in the early stages of the reaction. Without resorting to the particular physics of a non-equilibrium steady state,[39,40] the spontaneous asymmetric amplification in the Mannich reaction could be understood from two basic assumptions in accord with the well-known Frank mechanism of spontaneous asymmetric amplification: first, the assistance of an asymmetric product in the configuration determining step of the reaction, and secondly, the greater stability of the product heterodimer. Our earlier reports on spontaneous symmetry breaking in the Mannich reaction with acetone could be further confirmed by polarimeter and HPLC measurements, showing again that the counter-intuitive ee generation under formally achiral conditions is indeed possible. It remains to be seen, whether this previously overlooked phenomenon could be found in other stereoselective reactions. It is conceivable that reaction protocols might be developed in the future, which allows us to exploit this novel and remarkable effect.

4. Experimental

4.1. General

Solvents were purified by standard procedures and distilled prior to use. Reagents obtained from commercial sources were used without further purification. TLC chromatography was performed on precoated aluminium silica gel ALUGRAM SIL G/UV254 plates (Macherey, Nagel & Co.). Flash chromatography was performed using silica gel ACROS 60 Å, (particle size 0.035–0.070 mm). ^{1}H NMR spectra were recorded in $CDCl_3$ with Bruker Avance 300 or 400. Enantioselectivities were determined by chiral HPLC analysis (Daicel Chiralpak IA, *i*-Propanol/*n*-Hexane = 5:95; 4:96, flow rate 1.0 mL/min, λ = 254 nm) in comparison with authentic racemic material. Optical rotations were determined on a PerkinElmer polarimeter, model 341, λ = 589 nm.

4.2. Synthetic procedures

4.2.1. *N*-PMP-protected α-imino ethyl glyoxylate

A solution of ethyl glyoxylate (0.198 mL, 1.00 mmol) (50% in toluene) was slowly added to a stirring solution of *p*-anisidine (100 mg, 0.810 mmol) in dry CH_2Cl_2 (1.40 mL) with a syringe pump within 1 h with additional preactivated 4 Å molecular sieves (1.50 g). After the reaction mixture was stirred at 40°C for 3.5 h, the mixture was filtered and the solvent from the filtrate was evaporated under reduced pressure to afford an almost pure product. Further purification by column chromatography on silica gel under nitrogen using dry methylene chloride as an eluent gave the imine as a viscous yellow oil in 93% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm]: 7.94 (s, 1H, N=*CH*), 7.37 (d, *J* = 8.99 Hz, 2H), 6.95 (d, *J* = 8.98 Hz, 2H), 4.44 (q, 2H, *J* = 7.13 Hz, O*CH*$_2$CH$_3$), 3.86 (s, 3H, *CH*$_3$O), 1.43 (t, 3H, *J* = 7.13 Hz, OCH$_2$*CH*$_3$).

4.2.2. General procedure for the spontaneous symmetry breaking reaction between *N*-PMP protected α-imino ethyl glyoxylate and hydroxyacetone

A solution of *N*-PMP-protected α-imino ethyl glyoxylate (102,8 mg, 0.496 mmol, 1 equiv) in different solvents (c (educt) = 0.1–0.5 mol/L) was stirred with hydroxyacetone at room temperature for 1 to 6 h. The solvent was evaporated and the residue was purified by chromatography on a SiO_2-column (CH_2Cl_2/EtOAc/Petrolether, 1:1:1) and additional preparative TLC to afford the desired product (Table 1). Enantioselectivities were determined by chiral HPLC analysis (Daicel Chiralpak IA, *i*-Propanol/*n*-Hexane = 5:95; 4:96, flow rate 1.0 mL/min, λ = 254 nm) in comparison with authentic racemic material. ^{1}H NMR (400 MHz, $CDCl_3$,RT): δ [ppm]: 6.78 (d, *J* = 8.97 Hz, 2H), 6.62 (d, *J* = 8.99 Hz, 2H), 4.65 (bd, 1H, OH–*CH*), 4.48 (bd, 1H, NH–*CH*), 4.48 (bd, 1H, NH–*CH*), 4,22 (q, 2H, *J* = 7.11, O*CH*$_2$CH$_3$), 3.75 (s, 3H, *CH*$_3$O), 2.32 (s, 3H, CO–*CH*$_3$), 1.27 (t, 3H, *J* = 7.14 Hz, OCH$_2$*CH*$_3$–).

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