Electronic Supplementary Material (ESI) for Physical Chemistry Chemical Physics.

Supplementary Information

Spontaneous Emergence of Enantioenriched Chiral Aldol Reaction Products from Achiral Precursors in Solution and Origin of Biological Homochirality of Sugars: A First-Principles Study

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1. Frank Model of Figure 1

Hypothetical rate constants used:

$k_1 = 10^{-3}$ lmol^{-1}s^{-1}; $k_{-1} = 10^{-6}$ s^{-1}; $k_2 = 10^{-2}$ l^{2}mol^{-2}s^{-1}; $k_{-2} = 10^{-5}$ lmol^{-1}s^{-1}; $k_3 = 10^{-2}$ lmol^{-1}s^{-1}; $k_{-3} = 10^{-6}$ s^{-1}

Rate equations (100% enantioselectivity assumed, i.e. only homochiral autocatalytic steps are considered):

(1) $d[R]/dt = k_1[A]B] - k_{-1}[R] + k_2[R][A][B] - k_{-2}[R]^2 + k_3[R][S] - k_{-3}[RS]$

(2) $d[S]/dt = k_1[A]B] - k_{-1}[S] + k_2[S][A][B] - k_{-2}[S]^2 + k_3[R][S] - k_{-3}[RS]$

(3) $d[RS]/dt = k_3[R][S] - k_{-3}[RS]$

Particle number conservation (i.e. **closed system** conditions assumed):

$[A] = (101/100)_*[A]_0 - [R] - [S] - 2[RS]$;

$[B] = (101/100)_*[B]_0 - [R] - [S] - 2[RS]$

Initial chiral bias: $[R]_0 = 0.01$ moll^{-1}; $[A]_0 = [B]_0 = 1$ moll^{-1}

All other initial concentrations are zero.

2. Proof of Impossibility of Chiral Oscillations in the Frank Model of Scheme 1 due to existence of a Kinetic Potential:

The Frank mechanism (Scheme 1) in a simplified form with suppressed reaction partner **B**, consists of the following (reversible) steps:

$A + R \rightarrow R + R$

$A + S \rightarrow S + S$

$R + S \rightarrow P$

With prochiral reactant **A** and optically inactive product **P**. **R** and **S** are enantiomers. Concentration [A] is assumed to be clamped (implying an **open system**). When a kinetic potential is present, state variables (like concentrations) cannot assume the same state twice, precluding chiral oscillations.

When chiral oscillations occur, [R] grows at the cost of [S] and – at turns - vice versa, which is possible only, in principle, at a non-equilibrium steady state. Please note, that in SMSB, [R] grows instead monotonously at the cost of [S] - or vice versa - until one species becomes extinct.

Reaction velocities are (rate constants are suppressed):

(1) $V_1 = [A][R] - [R]^2,\ V_2 = [A][S] - [S]^2,\ V_3 = [R][S] - [P]$

And affinities (equilibrium constants and general gas constant are suppressed):

(2) $A_1 = \ln([A]/[R]),\ dA_1 = -\,d[R]/[R];\ A_2 = \ln([A]/[S]),\ dA_2 = -\,d[S]/[S];\ A_3 = \ln([R][S]/[P]),\ dA_3 = d[R]/[R] + d[S]/[S]$

Then it follows for the differential of the rate of internal entropy production with respect to the generalized forces (see for definitions SI section 6):

(3) $d_x\sigma = \Sigma_r\, v_r\, dA_r = ([A][R] - [R]^2) * (-d[R]/[R]) + ([A][S] - [S]^2) * (-d[S]/[S]) + ([R][S] - [P]) * (d[R]/[R] + d[S]/[S]) = -([A] - [R])d[R] - ([A] - [S])d[S] + ([S] - [P]/[R])d[R] + ([R] - [P]/[S])d[S] =$

$([S] - [P]/[R] - [A] + [R])d[R] + ([R] - [P]/[S] - [A] + [S])d[S]$

With the abbreviations

$\partial_x\sigma/\partial[R] = c_1$ and $\partial_x\sigma/\partial[S] = c_2$

this yields:

$\partial^2_x\sigma/\partial[R]\partial[S] = \partial/\partial[S]\,(c_1) = \partial/\partial[R]\,(c_2) = \partial^2_x\sigma/\partial[S]\partial[R] = 1$

Therefore we conclude (see SI section 6 for details), that a kinetic potential exists for the Frank model (with respect to the chemical composition as state function) and that, hence, chiral oscillations are precluded in this model (in contrast to, e.g., oscillations of species' populations in Lotka-Volterra type predator-prey models).[S1]

3. Cross-catalytic Model of Figure 2

Hypothetical rate constants used:

$k_1 = 10^{-3}$ lmol^{-1}s^{-1}; $k_{-1} = 10^{-6}$ s^{-1}; $k_2 = 10^{-3}$ l^{2}mol^{-2}s^{-1}; $k_{-2} = 10^{-6}$ lmol^{-1}s^{-1}; $k_3 = 10^{-1}$ l^{2}mol^{-2}s^{-1}; $k_{-3} = 10^{-5}$ lmol^{-1}s^{-1}; $k_4 = 10^{-3}$ lmol^{-1}s^{-1}; $k_{-4} = 10^{-6}$ s^{-1}; $k_5 = 10^{-1}$ l^{2}mol^{-2}s^{-1}; $k_{-5} = 10^{-5}$ lmol^{-1}s^{-1}; $k_6 = 10^{-3}$ l^{2}mol^{-2}s^{-1}; $k_{-6} = 10^{-6}$ lmol^{-1}s^{-1}

Rate equations (100% enantioselectivity assumed, i.e. only homochiral autocatalytic steps are considered):

(1) $d[R]/dt = k_1[A]B] - k_{-1}[R] + k_2[R][A][B] - k_{-2}[R]^2 + k_3[RR][A][B] - k_{-3}[RR][R]$

(2) $d[S]/dt = k_1[A]B] - k_{-1}[S] + k_2[S][A][B] - k_{-2}[S]^2 + k_3[SS][A][B] - k_{-3}[SS][S]$

(3) $d[RR]/dt = k_4[A][R] - k_{-4}[RR] + k_5[R]^2[A] - k_{-5}[R][RR] + k_6[RR][R][A] - k_{-6}[RR]^2$

(4) $d[SS]/dt = k_4[A][S] - k_{-4}[SS] + k_5[S]^2[A] - k_{-5}[S][SS] + k_6[SS][S][A] - k_{-6}[SS]^2$

Please note that the background reaction (not included in Scheme 2) is necessary to start autocatalysis. Eqs (1)-(4) represent an "explicit" cross-catalysis. Formation of achiral **RS** meso compound in heterochiral reactant autocatalytic reactions (Scheme 2) and which could also result from double addition is, for simplicity, not taken into account here, because we want to focus on the cross-catalysis itself.

Particle number conservation:

$[A] = (101/100)*[A]_0 - [R] - [S] - 2[RR] - 2[SS]$;

$[B] = (101/100)*[B]_0 - [R] - [S] - [RR] - [SS]$

Initial chiral bias: $[R]_0 = 0.01$ moll^{-1}; $[A]_0 = [B]_0 = 1$ moll^{-1}

All other initial concentrations are zero.

4. Kinetic Rate Equations with Boundary and Initial Conditions for Complete Model of Self-Catalyzed Aldol Reaction, Conforming to Scheme 4

Eqs.

(1) $d[R]/dt = k_1[A]B] - k_{-1}[R] + k_2[R][A][B] - k_{-2}[R]^2 + k_3[S][A][B] - k_{-3}[R][S] + k_4[RR][A][B] - k_{-4}[RR][R] + k_5[SS][A][B] - k_{-5}[SS][R] + (k_6 + k_7)[RS][A][B] - (k_{-6} + k_{-7})[RS][R]$

(2) $d[S]/dt = k_1[A]B] - k_{-1}[S] + k_2[S][A][B] - k_{-2}[S]^2 + k_3[R][A][B] - k_{-3}[R][S] + k_4[SS][A][B] - k_{-4}[SS][S] + k_5[RR][A][B] - k_{-5}[RR][S] + (k_6 + k_7)[RS][A][B] - (k_{-6} + k_{-7})[RS][S]$

(3) $d[RR]/dt = k_8[A][R] - k_{-8}[RR] + k_9[RR][A][R] - k_{-9}[RR]^2 + k_{10}[R]^2[A] - k_{-10}[R][RR] + k_{11}[S][R][A] - k_{-11}[S][RR] + k_{12}[SS][R][A] - k_{-12}[SS][RR] + (k_{13} + k_{14})[RS][R][A] - (k_{-13} + k_{-14})[RS][RR]$

(4) $d[SS]/dt = k_8[A][S] - k_{-8}[SS] + k_9[SS][A][S] - k_{-9}[SS]^2 + k_{10}[S]^2[A] - k_{-10}[S][SS] + k_{11}[S][R][A] - k_{-11}[R][SS] + k_{12}[RR][S][A] - k_{-12}[SS][RR] + (k_{13} + k_{14})[RS][S][A] - (k_{-13} + k_{-14})[RS][SS]$

(5) $d[RS]/dt = k_{15}[A]([R] + [S]) - 2k_{-15}[RS] + k_{16}[A]([R]^2 + [S]^2) - k_{-16}[RS]([R] + [S]) + 2k_{17}[R][S][A] - k_{-17}[RS]([R] + [S]) + k_{18}[RR][R]A] + k_{18}[SS][S][A] - k_{-18}[RR][RS] - k_{-18}[SS][RS] + 2k_{19}[RS][R][A] - 2k_{-19}[RS]^2 + k_{20}[RR][S][A] + k_{20}[SS][R][A] - k_{-20}[RS]([RR] + [SS]) + 2k_{21}[RS][S][A] - 2k_{-21}[RS]^2$

(6) $d[\mathit{RS}]/dt = k_{22}[R][S] - k_{-22}[\mathit{RS}]$

(7) $d[\mathit{RR}]/dt = k_{23}[R]^2 - k_{-23}[\mathit{RR}]$

(8) $d[\mathit{SS}]/dt = k_{23}[S]^2 - k_{-23}[\mathit{SS}]$

Because we assume a **closed system**, particle number conservation has to be observed as boundary condition:

(9) $[A] = [A]_0 - [R] - [S] - 2([RR] + [SS] + [RS] + [\mathit{RS}] + [\mathit{RR}] + [\mathit{SS}])$

(10) $[B] = [B]_0 - [R] - [S] - [RR] - [SS] - [RS] - 2([\mathit{RS}] + [\mathit{RR}] + [\mathit{SS}])$

Initial conditions are: $[A]_0$ variable, but ≥ 1 moll^{-1}, $[B]_0 = 1$ moll^{-1}, $[S]_0 = 0$ or 10^{-n} moll^{-1} (n = 2, 3 or 4).

Initial chiral bias is introduced, as if it had formed instantaneously from the reactants before reaction start:

E.g. for $[S]_0 = 10^{-2}$ moll^{-1}: $[B]'_0 = 1.01 * [B]_0$, $[A]'_0 = 1.01 * [A]_0$

When **A** is in excess, $[A]_0$ is set to, e.g., hypothetical concentration of 10 moll^{-1} for a 10:1 ratio of A to B

5. Calculated Kinetic Rate Constants of Scheme 4 for Complete Model of Self-Catalyzed Aldol Reaction:

$k_1 = 6.03*10^{-3}\ \mathrm{lmol^{-1}s^{-1}}$, $k_{-1} = 1.55*10^{-6}\ \mathrm{s^{-1}}$,

$k_2 = 3.07*10^{-3}\ \mathrm{l^2mol^{-2}s^{-1}}$, $k_{-2} = 7.92*10^{-7}\ \mathrm{lmol^{-1}s^{-1}}$,

$k_3 = 2.32*10^{-2}\ \mathrm{l^2mol^{-2}s^{-1}}$, $k_{-3} = 5.99*10^{-6}\ \mathrm{lmol^{-1}s^{-1}}$,

$k_4 = 1.75*10^{-4}\ \mathrm{l^2mol^{-2}s^{-1}}$, $k_{-4} = 4.50*10^{-8}\ \mathrm{lmol^{-1}s^{-1}}$,

$k_5 = 2.59*10^{-3}\ \mathrm{l^2mol^{-2}s^{-1}}$, $k_{-5} = 6.69*10^{-7}\ \mathrm{lmol^{-1}s^{-1}}$,

$k_6 = 1.66*10^{-2}\ \mathrm{l^2mol^{-2}s^{-1}}$, $k_{-6} = 3.61*10^{-6}\ \mathrm{lmol^{-1}s^{-1}}$,

$k_7 = 7.92*10^{-7}\ \mathrm{l^2mol^{-2}s^{-1}}$, $k_{-7} = 1.73*10^{-10}\ \mathrm{lmol^{-1}s^{-1}}$,

$k_8 = 2.73*10^{-5}\ \mathrm{lmol^{-1}s^{-1}}$, $k_{-8} = 1.31*10^{-6}\ \mathrm{s^{-1}}$,

$k_9 = 5.36*10^{-5}\ \mathrm{l^2mol^{-2}s^{-1}}$, $k_{-9} = 2.58*10^{-6}\ \mathrm{lmol^{-1}s^{-1}}$,

$k_{10} = 8.39*10^{-6}\ \mathrm{l^2mol^{-2}s^{-1}}$, $k_{-10} = 3.41*10^{-7}\ \mathrm{lmol^{-1}s^{-1}}$,

$k_{11} = 8.34*10^{-9}\ \mathrm{l^2mol^{-2}s^{-1}}$, $k_{-11} = 3.39*10^{-10}\ \mathrm{lmol^{-1}s^{-1}}$,

$k_{12} = 2.90*10^{-4}\ \mathrm{l^2mol^{-2}s^{-1}}$, $k_{-12} = 1.39*10^{-5}\ \mathrm{lmol^{-1}s^{-1}}$,

$k_{13} = 1.47*10^{-7}\ \mathrm{l^2mol^{-2}s^{-1}}$, $k_{-13} = 7.05*10^{-9}\ \mathrm{lmol^{-1}s^{-1}}$,

$k_{14} = 1.24*10^{-7}\ \mathrm{l^2mol^{-2}s^{-1}}$, $k_{-14} = 5.95*10^{-9}\ \mathrm{lmol^{-1}s^{-1}}$,

$k_{15} = 7.09*10^{-6}\ \mathrm{l^2mol^{-2}s^{-1}}$, $k_{-15} = 1.47*10^{-7}\ \mathrm{lmol^{-1}s^{-1}}$,

$k_{16} = 2.72*10^{-8}\ \mathrm{l^2mol^{-2}s^{-1}}$, $k_{-16} = 5.62*10^{-10}\ \mathrm{lmol^{-1}s^{-1}}$,

$k_{17} = 1.75*10^{-4}\ \mathrm{l^2mol^{-2}s^{-1}}$, $k_{-17} = 3.61*10^{-6}\ \mathrm{lmol^{-1}s^{-1}}$,

$k_{18} = 1.94*10^{-8}\ \mathrm{l^2mol^{-2}s^{-1}}$, $k_{-18} = 4.01*10^{-10}\ \mathrm{lmol^{-1}s^{-1}}$,

$k_{19} = 8.39*10^{-6}\ \mathrm{l^2mol^{-2}s^{-1}}$, $k_{-19} = 1.74*10^{-7}\ \mathrm{lmol^{-1}s^{-1}}$,

$k_{20} = 1.11*10^{-6}\ \mathrm{l^2mol^{-2}s^{-1}}$, $k_{-20} = 2.29*10^{-9}\ \mathrm{lmol^{-1}s^{-1}}$,

$k_{21} = 2.86*10^{-10}\ \mathrm{l^2mol^{-2}s^{-1}}$, $k_{-21} = 5.92*10^{-12}\ \mathrm{lmol^{-1}s^{-1}}$,

$k_{22} = 6.77*10^{0}\ \mathrm{lmol^{-1}s^{-1}}$, $k_{-22} = 1.00*10^{-1}\ \mathrm{s^{-1}}$,

$k_{23} = 2.60*10^{-1}\ \mathrm{lmol^{-1}s^{-1}}$, $k_{-23} = 1.00*10^{0}\ \mathrm{s^{-1}}$,

6. Proof of Absence of a Kinetic Potential in Terms of the Thermodynamics of Non-linear Irreversible Processes for Cross-Catalytic Model of Scheme 2:

Chemical potential μ for component with index i in a reaction mixture (with all other molar quantities n_j fixed) is defined as:[S2]

(1) $\mu_i = (\partial G/\partial n_i)_{S,V,nj \neq ni}$

(with Gibbs free energy G, molar quantity n, fixed Entropy S and fixed volume V)

Generalized forces X_r for reaction with index r and absolute temperature T is:

(2) $X_r = -A_r/T$

With chemical affinity at non-equilibrium for an ideal mixture

(3) $A_r = RT{*}\ln(K_r{*}\prod c_i^{\nu i}) = - (\partial G/\partial \xi_r)_{p,T}$

(with general gas constant R, equilibrium constant K, concentration of component c, respective stoichiometric coefficient ν_i, De Donder reaction variable ξ, pressure p). Hence: $A_r\, d\xi_{ir} = \mu_i\, \nu_i\, d\xi_{ir} = \mu_i\, dn_{ir}$

Entropy production б in irreversible thermodynamics is given by:[S3]

(4) $\text{б} = d\Delta S_i/dt = \Sigma_j X_j J_j$

(with change in internal entropy ΔS_i, generalized flows J).

б is zero for a chemical equilibrium, because the argument in the logarithm in (3) becomes unity, and all $X_j = 0$, even if $J_j \neq 0$.

The differential for б with respect to generalized forces in the general case of non-linear reactions becomes:

(5) $d_x\text{б} = \Sigma_j J_j dX_j$

The non-linearity goes back to the reactant (or indirect product) autocatalytic reactions in Scheme 2. Please note, that one cannot generally assume here that $J_j = L_{ji} * X_i$, with a symmetric matrix of phenomenological coefficients $L_{ji} = L_{ij}$, as for irreversible thermodynamics of linear processes. If 1-form (5) is not a total (or exact) differential, there is, in general, no kinetic potential for the reaction network, which means that the integral of (5) becomes path-dependent and chemical oscillations become possible.

Generalized flows in a chemical reaction are the reaction velocities v_r. Because of (2) and (3), (5) becomes

(6) $T{*}d_x\text{б} = \Sigma_r v_r\, dA_r$

For a total (or exact) differential to hold, is $d_x\text{б} = \Sigma_r (\partial_x\text{б}/\partial A_r){*}dA_r$

Because $dA_r = RT{*}\ d\ln(\prod c_i^{\nu i})$, and when we assume conditions of a **flow reactor** with clamped concentrations c_j (here: the reactant concentrations [A] and [B]), the condition for $d_x\text{б}$ to be a total differential becomes because of (3):

(7) $d_xб = \Sigma_i\, (\partial_x б/\partial c_i)_{cj\,*}\, \nu_i\, dc_i$ for all variable concentrations $c_i \neq c_j$

The same is true when no concentrations are clamped, but the following derivation would become more involved. Please note that, exchange entropy flows over the open system boundary due to clamping are not taken into account. Hence, $d_xб$ does only include the internal entropy production rate going back to chemical reactions in the system. In addition, and under non-isothermal conditions, entropy export may also occur, of course, as in a closed system (e.g., when environment temperature is lower than system temperature and exothermic reactions run inside the system).

In the following, all constants are suppressed (namely rate constants k_i, equilibrium constants K_r, and the general gas constant R). We assume the cross-catalytic reaction network of Scheme 2 to hold.

Equation (7) holds only when all mixed partial derivatives $(\partial^2{}_x б/\partial c_i \partial c_j)$ for every given $(c_i,\ c_j)$ pair commute:

(8) $\partial^2{}_x б/\partial c_i \partial c_j = \partial^2{}_x б/\partial c_j \partial c_i$

In order to show that there is, in general, no kinetic potential for the reaction network of Scheme 2, it has to be shown at least for one $(c_i,\ c_j)$ pair that (8) does not hold, here taken to be the enantiomer concentrations of single-aldol addition product [R] and [S].

Reaction velocities are:

(9) $V_1 = [A][B][RR] - [R][RR]$, $V_2 = [A][B][SS] - [S][SS]$, $V_3 = [R]^2[A] - [RR][R]$, $V_4 = [S]^2[A] - [SS][S]$, $V_5 = [R][A][S] - [RS][S]$, $V_6 = [R][A][S] - [RS][R]$

And affinities:

(10) $A_1 = \ln([A][B]/[R])$, $dA_1 = -\,d[R]/[R]$; $A_2 = \ln([A][B]/[S])$, $dA_2 = -\,d[S]/[S]$; $A_3 = \ln([A][R]/[RR])$, $dA_3 = -\,d[R]/[R] - d[RR]/[RR]$; $A_4 = \ln([A][S]/[SS])$, $dA_4 = -\,d[S]/[S] - d[SS]/[SS]$; $A_5 = \ln([A][R]/[RS])$, $dA_5 = -\,d[R]/[R] - d[RS]/[RS]$; $A_6 = \ln([A][S]/[RS])$, $dA_6 = -\,d[S]/[S] - d[RS]/[RS]$

After insertion of (9) and (10) in (6), addition and re-ordering of terms, coefficients in (7) become

$c_R = \partial_x б/\partial[R] = [R][A] - [A][B][RR]/[R] + [A][S] - [RS][S]/[R]$ and

$c_S = \partial_x б/\partial[S] = [S][A] - [A][B][SS]/[S] + [A][R] - [RS][R]/[S]$

and, hence:

(11) $\partial^2{}_x б/\partial[R]\partial[S] = [A] - [RS]/[R] \neq \partial^2{}_x б/\partial[S]\partial[R] = [A] - [RS]/[S]$

Therefore we conclude that, in general, no kinetic potential exists for the cross-catalysis network shown in Scheme 2. Please note, that at thermodynamic equilibrium, because of [R] = [S], $\partial^2{}_x б/\partial[R]\partial[S] = \partial^2{}_x б/\partial[S]\partial[R]$ and chemical oscillations are hence, of course, impossible.

When not all v_r in $\Sigma_r v_r = 0$ vanish individually, a non-equilibrium steady state (NESS) is assumed. When we assume that the generalized flows are constant in time (i.e. $dJ_j = 0$), the relationship

(12) $d_xб/dt = \Sigma_j J_j\, (dX_j/dt) \leq 0$

holds, and which is called “evolution criterion”. It should not be confused with the “**principle of minimal entropy production**”,[S4] which holds for discrete NESS close to equilibrium and is based on linear irreversible processes and which refers to the change of б(J_i,X_j) under variation of forces ΔX_j, and can be considered a generalization of Le Chatelier's principle to non-equilibrium steady states. Please note that flows are dependent on forces.

For linear systems, the more strict dб/dt ≤ 0 holds, rather than (12), i.e. a linear transient system must develop in time either towards an equilibrium state or to a local minimum of entropy production. Racemic states must therefore be always local minima of entropy production. But the converse is not true. Non-racemic states may therefore also be located at local minima of б, as well, but cannot develop in linear reaction networks. The Brussels school assumed a wide applicability of the minimum entropy production principle. However, Keizer and Fox have shown in 1974, that in autocatalytic systems, the principle is not generally valid far from equilibrium.[S5]

Only for non-linear systems (e.g. that of scheme 2), (12) may be interpreted instead as resulting from a hypothetical "**principle of maximum entropy production**", which means that at least some NESS, once attained, could be characterized by a local maximum, rather than a minimum, in entropy production б(J_j,X_j). It is therefore conceivable that transient non-linear systems may be driven towards such a - kinetically stable - local maximum of entropy production (in apparent contradiction to the evolution criterion), provided that enough energy is available. At such a state, any variation of forces ΔX_j, must result in a decrease in entropy production rate. The physics behind the evolvement of transient states of non-linear systems towards such local maxima of б, has not been established yet, though. There is, however, some empirical evidence for such a maximum entropy production principle (but not yet with respect to time development of transient states), at least for non-discrete NESS outside of the chemistry domain.[S6]

For example, the earth's biosphere, which is an open non-linear driven system that receives energy supply from the sun, the molten core of the planet and the heat released in radioactive decay of elements in the earth's crust, is assumed to constantly develop towards a maximum-б non-equilibrium state.[S7]

The condition of constant flows is no longer valid when we are in a transient state or depart too far from the NESS, i.e. we assume here that the entropy production can be developed around the NESS as a Taylor expansion.

7. Effect of Asymmetric Reactant Autocatalysis (of Scheme 2 and 4) on Enantiomeric Purity and Reactant Cross-Catalysis

6.1. Asymmetric Reactant Autocatalysis

We consider the following double-addition reaction steps with enantiomers **R** and **S** (see, e.g., processes with rate constants k_{10}, k_{11}, k_{16} and k_{17} in Scheme 4), as they occur in Scheme 2 or 4 (catalytically active species are in italics, respectively):

(1) A + R + *R* → RR + *R* , (2) A + R + *R* → RS + *R*, (3) A + S + *S* → RS + *S*, (4) A + S + *S* → SS + *S*

and (5) A + R + *S* → RS + *S*, (6) A + S + *R* → RS + *R*, (7) A + R + *S* → RR + *S*, (8) A + S + *R* → SS + *R*,

Steps (1) – (4) are homochiral, because reactant and catalyst possess the same absolute configuration, steps (5) - (8) are heterochiral.

Please note, that such **directly reactant autocatalytic** processes are relevant here only in double-addition steps, i.e. when either (already formed) single-aldol product **R** (or **S**) is also reactant (because we consider only chiral matter to exert a catalytic effect herein).

For achiral "reactant autocatalysts", above reaction equations simplify; and in this case, also single-addition steps could be taken into account. For instance, hypothetical exergonic reaction 2 R → A + R (component B is suppressed for clarity) is a spontaneous reactant (auto)catalyzed (= promoted) decay process of substrate **R**. Therefore, considerations as outlined here, can principally also be applied to other chemical processes as well, of course.

We assume in the following (without restriction of generality) that all these above steps (1) – (8) are even faster than any of the background reactions (9) – (12) (i.e catalysis is positive, the presence of an additional **R** or **S** molecule in the transition state structure is assumed to lower the activation barrier for the net process):

(9) A + R → RR, (10) A + S → SS , (11) A + S → RS, (12) A + R → RS

Note, that only the homochiral reactant autocatalytic steps, (1) - (4), are self-decelerating, i.e. where reactant and catalyst have the same absolute configuration and the catalyst facilitates its own consumption. In contrast, rate does NOT change in heterochiral steps (5) - (8), because **R** (reactant) and **S** (catalyst), or vice versa, are not the same species!

As **R** and **S** are enantiomers, we consider first their stereoinductive effect, i.e. when they act as chirality inducers in the activated complex as in asymmetric catalysis (i.e. here: "asymmetric autocatalysis"). This results, e.g., in a certain positive or negative enantioselectivity for (1) and (2), depending on whether (1) is faster than (2), or vice versa, respectively. Please note that the difference in reaction velocity of (1) and (2) only depends on the effect of ***R*** (catalyst) on the activation barriers in these steps, as their left-hand sides are equal.

We assume in this work that no double-addition products are included in definition of ee value (e.g., to take into account in a single order parameter the whole chiral matter produced or consumed), as in

(13) $ee_{total} = [(R + RR) – (S + SS)] / (R + RR + S + SS)$

Moreover, we consider only ee value for single-addition products: $ee_s = ee = R – S / (R + S)$ and not an additional one for double-addition products as well, i.e. $ee_d = (RR – SS) /(RR + SS)$. Hence, ee (i.e. ee_s) value will not increase, but rather decrease (i.e. constitute a chiral depletion), through homochiral reactant autocatalytic steps (1)-(4), because rate of consumption of **R** (or **S**) is always proportional to $[R]^2$ (or $[S]^2$), respectively: $d[R]/d[S] = - ([R]/[S])^2$, cf. positivity of differential quotient in Blackmond-Brown mechanism (Scheme 1). This means, that any possibly existing chiral amplification mechanism is actually impeded (!) by such (non-linear and spontaneous) reaction steps: the higher the ee value is, the faster it erodes through such processes as (1) – (4).

Now we consider heterochiral reactant (asymmetric) autocatalytic steps (5) - (8), which are not self-decelerating in contrast to their homochiral variants. Meso-form **RS** is optically inactive. At first glance, such a process, like (5), is reminiscent of a Frank-type mutual inhibition. However, because reaction velocity depends on product $[R]*[S]$ with **R** (reactant) and **S** (catalyst), or vice versa in the mirror image process, any potential increase in ee value is cancelled out by the mirror image process (note also that product $[R]*[S]$ is maximal for the racemic composition). There is no net effect on the ee value.

We conclude, that reactant autocatalytic processes cannot enhance the enantiomeric excess of a reaction mixture, when reactant/catalyst is a chiral species, provided only their concentrations are used to define the order parameter of the reaction mixture. Nevertheless, these processes must be taken into account in a mathematical modelling of the reaction as well, because they transform chiral matter. Without them, any mathematical model of a reacting system wouldn't be complete!

6.2. Reactant Cross-Catalysis

Cross-catalysis can also be considered a coupled system of two indirectly product autocatalytic reactions, as e.g. can be seen from Scheme 2. But chemistry allows also for **indirectly reactant autocatalytic** (or reactant cross-catalytic) processes:

Consider, for example, the following - not necessarily stereoselective – reactions:

(14) $A + B + F \rightarrow D + F$ (with reactant **B** and catalyst **F**) and

(15) $E + F + B \rightarrow C + B$ (with reactant **F** and catalyst **B**)

The above system is obviously cross-catalytic, because, in none of the two reactions is product also catalyst. Moreover, the catalysts are not product of the respective other reaction either. Therefore, (14) and (15) constitute a reactant cross-catalytic system, which however, results soon after reaction start in a deadlock situation, because the two reactions mutually block each other's progress.

Notwithstanding, if there is also an additional production reaction for either of the reactant/catalysts in (14) or (15), or an impact of the concentrations of products **C** or **D** on other reactions in a coupled system, it is not recommendable to neglect such processes in a reaction simulation.

8. Computational Methods

We used density functional theory (DFT) for geometry optimization without any geometry restrictions and with the GAUSSIAN09 quantum chemistry program suite.[S8] Unless otherwise stated, B3LYP/6-31G* level had been used throughout, with Becke's three parameter functional[S9] and the correlation correction of Lee, Yang and Parr.[S10] Pople's et al. valence split basis sets have been used throughout.[S11] All stationary points (minima and transition states) on their respective potential energy surfaces (PES) had been rigorously characterized by the number of imaginary frequencies in harmonic frequency calculations. Relative energies are zero-point energy (ZPE) corrected throughout. Thermodynamic correction to internal energies have been applied to obtain Gibbs free energies, based on the result of frequency computations. Transition state structures have been matched to their pertaining minimum structures by an intrinsic reaction coordinate (IRC) following algorithm. To evaluate the size of the error we make in not using a more sophisticated approach, we benchmarked our chosen level of theory by including solvent and dispersion effects in the calculation of reaction energies and activation barriers for the uncatalyzed single aldol addition step with the 6-311+G** basis set. In order to take into account dispersion energy effects, Grimme's D3 semi-empirical dispersion energy correction has been used, together with Becke-Johnson damping, to facilitate convergence.[S12] Solvent effects had been taken into account by using Tomasi's polarizable continuum model (PCM) for solvent DMSO (dielectric constant ε_r = 46.8).[S13] Activation barriers and dimerization equilibrium constants have been calculated by assuming separated reactants without correcting for the basis set superposition error (BSSE). The BSSE correction in following this approach, i.e. when computing binding energies in hydrogen bonded complexes, is assumed to be small and often less than the size of corrections for solvent or dispersion effects and tends to increase the activation barrier and lowers the dimerization enthalpy.[S14] Cartesian coordinates of all species can be requested from the authors. Numerical simulations have been carried out with Mathematica© from Wolfram Research.

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