#### PERSPECTIVE



# **Chiral Autocatalysis and Mirror Symmetry Breaking**

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#### Abstract

Highly enantioselective production of chiral compounds by chiral catalysis is one of the most challenging forms of catalytic selectivity. In this perspective, we argue by examples that the key to achieving high enantioselectivity lies in processes with non-linear kinetics or equilibria that effectively amplify small differences in enantiospecific energetics. Examples of such processes have been uncovered over the past decade and include autocatalysis, surface explosion reactions, stirring or grinding of crystallites, and cooperative self-assembly.

#### **Graphical Abstract**



Keywords Chirality  $\cdot$  Enantioselectivity  $\cdot$  Autocatalysis  $\cdot$  Surface explosion  $\cdot$  Sergeants-and-soldiers  $\cdot$  Mirror symmetry breaking  $\cdot$  Chiral amplification

## 1 Introduction

Enantioselective catalysis is arguably one of the most challenging forms of catalysis. In large part, the challenge lies in the fact that the enantiospecific energy differences between the interactions of two enantiomers with a chiral catalyst

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tend to be relatively small (a few kJ/mol) [1]. Consequently, the enantiospecific differences in the rate constants and equilibrium constants that determine catalytic enantioselectivity are also relatively small. While selectivity is critical to most commodity scale catalytic processes, selectivity to specific enantiomers of chiral compounds is of critical importance in the production pharmaceuticals, agrochemicals, and other fine chemicals used in bioactive applications. The importance of enantioselectivity arises from the fact that most of the biochemicals on which terrestrial life is based are chiral but only appear in one enantiomeric form in nature [2]. Basically, all naturally occurring amino acids are L-enantiomers, while the sugars of natural DNA and RNA are always found as D-enantiomers. Just as the right and left hand fit into a right-handed glove differently, the two enantiomers of a chiral pharmaceutical interact differently with single-handed proteins and enzymes formed purely of L-amino acids. While one enantiomer of an ingested chiral compound can be therapeutic, the opposite enantiomer can be toxic [3]. Because separation of the two enantiomers is challenging, it is desirable that chiral pharmaceuticals be produced for market in enantiomerically pure form by highly enantioselective processes.

Homogeneous catalysts are more prevalent than heterogeneous catalysts in enantioselective chemical processes. Nonetheless, enantioselective chiral heterogeneous catalysts have inherent potential advantages over homogenous catalysts. Heterogeneous catalysts rely on the use of chiral solid surfaces and their enantioselective surface chemistry. Chiral solid surfaces are also used as the basis for enantioselective chemical processes such as adsorption-based separations and crystallization. Equally importantly, chiral surfaces have been the focus of intense model studies revealing fundamental aspects of chiral surface chemistry [4, 5].

There are two primary means by which one can generate chiral surfaces [5, 6]. The first is the adsorption of enantiomerically pure chiral organic compounds onto otherwise achiral surfaces. The second is the preparation of crystalline inorganic surfaces from chiral materials or from achiral materials such as metals. Preparation of single crystalline metal surfaces whose normals do not lie in any of the bulk mirror planes results in chiral surfaces with two enantiomers (Fig. 1) [7, 8]. All of these types of chiral surfaces have interactions with chiral adsorbates that exhibit enantiospecific adsorption energies, reaction energies and reaction barriers. Such enantiospecific adsorbate–surface interactions are at the root of all catalytic reaction kinetics and serve as the origin of enantioselective adsorption and catalysis.

One of the key obstacles to highly enantioselective chemistry is the limited enantiospecificity of the rate constants and equilibrium constants associated with the reactions of chiral compounds in chiral environments such as surfaces, catalysts, sorbents, etc. The enantiospecificities of most such interaction energies are on order of a few kJ/mol [1, 9–14]. At 300 K, an energy difference of 1 kJ/mol translates into an enantiospecificity of just ~ 1.5. Consider the reaction of an



**Fig. 1** Ball models of the  $(643)^{R}$  and  $(643)^{S}$  planes of an FCC metal. The structures can be described as (111) terraces with (100) steps and (111) kinks. Their chirality arises from rotational ordering of the (111), (100) and (110) microfacets around the kinks. The two structures are enantiomorphs, i.e. non-superimposable mirror images of one another [8]

achiral molecule, A, to form the two enantiomers, *R*-P and *S*-P, of a chiral product

$$A \xrightarrow{k_R} R$$
-P and  $A \xrightarrow{k_S} S$ -P.

In an achiral environment  $k_R = k_S$  and the two enantiomers are produced as a racemic (equimolar) mixture. In the presence of a chiral catalyst, *R*-C or *S*-C,

A 
$$\stackrel{k_{R/S}}{\xrightarrow{}}_{S-C}$$
 *R*-P and A  $\stackrel{k_{S/S}}{\xrightarrow{}}_{S-C}$  *S*-P

the rate constants will be enantiospecific,  $k_{S/R} = k_{R/S} \neq k_{S/S} = k_{R/R}$ , and the two enantiomers will be produced at different rates. However, if the rate constants only differ by a factor of 1.5, the enantiomeric excess (*ee*) in the product mixture will only be

$$ee = \left| \frac{k_{R/S} - k_{S/S}}{k_{R/S} + k_{S/S}} \right| = 0.2$$

and the product mixture would require significant enantiopurification. Even if the free energy barriers dictating the values of the rate constants differ by as much as 5 kJ/mol, the rate constants differ by a factor of just 7.4 at 300 K and the enantiomeric excess in the product mixture only reaches ee = 0.76. Circumventing these limitations in the enantiospecificities of chiral reactions is the primary challenge to the development of viable heterogeneous enantioselective chemical processes.

The limitations mentioned above are dictated by the inherent kinetics of the processes being used, if they are limited to simple zero-, first- or second-order reactions or equilibria. Overcoming these limitations calls for processes that are inherently highly non-linear [15, 16]. Chiral chromatography is a good example of a successful process leading to enantioselective separations [17]. The two enantiomers of a chiral compound elute from a column packed with a chiral stationary phase with significantly different retention times. In spite of the fact that the inherent difference in the heats of adsorption of the two enantiomers on the chiral stationary phase are quite small and a single adsorption/desorption step would yield rather low enantiospecificity, the numerously repeated adsorption/desorption steps occurring during transport along the column can lead to highly enantioselective separations. This results from the fact that, in its implementation, chromatography is a highly non-linear process.

Non-linear kinetics can arise from a variety of causes. In homogeneous systems, explosions are considered non-linear. The simplest would be a thermal explosion in which an exothermic reaction releases heat at a rate greater than that at which it can be extracted from the reaction volume [18]. As a result, the reaction temperature increases, increasing the reaction rate constants and the rate of heat release, creating positive feedback and a runaway reaction. In catalysis, there are many examples of such processes that exhibit 'light-off' once the temperature reaches a certain value during heating [19–21]. As a second example of a highly non-linear process, the mechanisms of gas phase explosions commonly exhibit radical branching steps in which one radical creates two which then create four, eight, sixteen etc. resulting in an undamped, exponential increase in radical concentration [22]. Under the wrong conditions, the oxidation of hydrogen can be explosive because of undamped production of H-radicals via the following radical branching steps:

$$H \cdot + O_2 \rightarrow HO \cdot + O \cdot$$

$$O \cdot + H_2 \rightarrow HO \cdot + H \cdot$$

$$HO \cdot + H_2 \rightarrow H \cdot + H_2O$$

In surface reactions non-linear kinetic effects can arise from interactions between adsorbates leading to coveragedependent reaction barriers and rate constants. For example, if a reaction barrier were to decrease with decreasing reactant coverage,  $\Delta E^{\ddagger}(\theta) = \Delta E_0^{\ddagger} + \epsilon \theta$ , even an isothermal first-order reaction with  $r = k\theta$  would exhibit an acceleration in reaction rate as the extent of reaction increased (adsorbate coverage,  $\theta$ , decreases). Phenomena like these can be harnessed to yield high enantioselectivity in processes with rate constants and equilibrium constants having low inherent enantiospecificity.

The past decade has witnessed the discovery of a number of non-linear surface phenomena that can serve as the basis for highly enantioselective heterogeneous chemical processes including separations, crystallization and catalysis. Herein, we present the current understanding of a number of these phenomena. We do so to make the case that in the field of enantioselective catalysis they offer a route to high enantioselectivity that warrants further investigation.

#### 2 The Soai Reaction

The first simple model of chiral autocatalysis was presented by Frank in 1953, who proposed in an open system (i) linear autocatalytic production of enantiomers of the type  $A + R-P \rightarrow 2R-P$  and  $A + S-P \rightarrow 2S-P$ , and (ii) annihilation of opposite enantiomers into inactive dead-end byproducts (i.e.  $R-P + S-P \rightarrow RS-P_2$ ) which effectively leave the system [23]. In other words, both enantiomers simultaneously copy themselves while destroying their mirror images. Frank showed that an initial enrichment of one enantiomer by statistical fluctuation will lead to total enrichment of that enantiomer by linear autocatalysis. This is one of the types of mechanisms that has been suggested to have led to the homochirality of life on Earth [24]. The theoretical scenario of Frank, as an attempt to explain the homochirality of life, found no experimental analogue until 1990, when Soai reported an extremely efficient autocatalytic chiral reaction [25]. It is the prototypical example of asymmetric autocatalysis,  $A + R-P \rightarrow 2R-P$  and  $A + S-P \rightarrow 2S-P$ , in which both the atomistic connectivity and the handedness of the product are identical to that of the molecular catalyst [26].

This reaction has been studied extensively by various research groups around the world because it yields enantiomeric excess with high efficiency and selectivity, thereby effectively amplifying enantiopurity. In spite of many efforts to find other chemical systems with these characteristics, there has been limited success and no improvement over the Soai reaction [26–28]. Soai and others have studied many variations of this reaction in which the nature of the pyrimidine ring and the alkyl groups on the organozinc reagent have been modified. While many variations on the pyrimidine yield significant enantioselective auto-amplification, the isopropyl group is clearly the most effective ligand on the organozinc [25, 29–31].

The mechanism of the Soai reaction has been clearly demonstrated to have the characteristics of enantioselective autocatalysis, but the mechanism is still not fully understood and is likely to be more complex than the original model for simple asymmetric autocatalysis put forward by Frank [23]. It has been suggested that the product dimerizes in solution, preferentially forming heterochiral dimers over homochiral dimers. In a non-racemic mixture, the minority enantiomer is consumed by the formation of the heterochiral dimers which are inactive catalysts. The remainder of the majority enantiomer is bound in homochiral dimers that are catalytically active for self-reproduction, hence leading to amplification of enantiomeric excess. One of the most interesting aspects of the Soai reaction is its stunning sensitivity to biases in the chirality of the reaction environment. As initially conceived and demonstrated, the reactant mixture included some fraction of the reaction product (2) as a catalyst. In the absence of the product/catalyst (2) the reactant (1) is alkylated very slowly. In the presence of racemic product (2S + 2R), alkylation is slow and yields only the racemic mixture. However, in the presence of small amounts of enantiomerically enriched



Scheme 1 Reagent 1 seeded with a small enantiomeric excess of autocatalyst 2S is combined with an excess of  $Zn(iPr)_2$ . Autocatalysis by 2S converts 1 into 2S with high *ee* 

product (2S), the reaction is accelerated catalytically and yields an excess of 2S (Scheme 1).

More interestingly, Soai has demonstrated that in the initial absence of any enantiomerically enriched product (2), one can observe the formation of enantiomerically enriched product by exerting a number of other chiral biases on the reaction. For example, seeding the reaction mixture with either *d*- or *l*-quartz results in the selective formation of product mixtures enriched in **2S** and **2R**, respectively (Scheme 2) [32].

It is important, to note that the quartz itself is not the enantioselective autocatalyst. The quartz is a chiral seed that biases the initial reaction by some heterogeneous process to produce a slight excess of one product enantiomer which in turn autocatalyzes its self-reproduction in the homogeneous solution phase. More recently, Soai et al. were able to show that addition of non-reactive chiral organic species to the reaction mixture is also sufficient to bias the reaction enantioselectively. In fact, the reaction is so sensitive that the enantiospecific bias can be at the level of an isotopic substitution [33]. While the Soai mechanism for autoamplification of enantiomeric excess is clearly homogeneous, the fact that it can be seeded with single enantiomers of quartz and then yield an enantiopure product implies that heterogeneous reaction steps play a role in providing the initial enantiomer bias that determines which product enantiomer is enriched in the final mixture.

#### 3 Chiral Autocatalysis in 2D: Surface Explosion

There are heterogeneous surface reactions with inherently non-linear kinetics analogous to those of autocatalysis. One well known example is the vacancy-mediated surface explosion mechanism first reported by Madix et al. during the decomposition of formate (HCOO) on Ni(110) into CO<sub>2</sub> and H<sub>2</sub> [34]. While heating HCOO/Ni(110) at a constant rate of 12 K/s they observed the desorption of CO<sub>2</sub> and H<sub>2</sub> in a peak at 388 K that spanned a very narrow temperature range of 6.5 K. This temperature range is far too narrow to be reasonably assigned to any simple first- or second-order kinetic



**Scheme 2** Even the small bias provided by the chiral surface sites of quartz determines the sign of enantiomeric excess in the autocatalytic Soai reaction

processes, as described by Redhead [35]. Instead Madix suggested that the decomposition process must occur by a step that requires the presence of a vacant adsorption site, \*, adjacent to the decomposing formate:

HCOO \* + \* 
$$\rightarrow$$
 CO<sub>2</sub> +  $\frac{1}{2}$ H<sub>2</sub> + 2 \*

The implied rate law would have the basic form

$$r = \frac{-d\theta}{dt} = k\theta(1-\theta)$$

where  $\theta$  represents the fractional coverage of HCOO on the Ni(110) surface. Madix surmised that when the initial formate coverage was close to  $\theta_0 = 1$  the rate would be vanishingly small were it not for the presence of some residual vacancies or defects in the formate monolayer. Once formed, by whatever means, these vacancies would 'autocatalyze' the formation of new vacancies. One vacancy would yield two, two would yield four, four yields eight, etc. resulting in a rapid acceleration of the reaction rate as  $(1 - \theta)$  increases and complete consumption of the adsorbed formate over a very narrow temperature range. They noted that this type of mechanism would imply that under isothermal conditions where the rate constants are not changing, one ought to observe an acceleration of the reaction rate over the initial course of the reaction. A subsequent publication, in which they coined the term 'surface explosion', demonstrated that this was indeed the case [36]. The vacancy-mediated surface explosion reaction mechanism is analogous to the gas phase radical branching mechanism of explosions [22], but on a surface, it is the vacancies that are self-replicating autocatalytically. In the years since their initial discovery, vacancy-mediated surface explosions have been observed for decomposition of formate and acetate on a variety of surfaces including single crystals and supported metal catalysts [37–39].

Independent temperature programmed reaction (TPR) studies by Ernst and Raval of the thermally induced decomposition of tartaric acid (TA, HOOC–CH(OH)–CH(OH)–COOH) on achiral Cu(110) also reported a surface explosion mechanism yielding predominantly CO<sub>2</sub> [40, 41]. Ernst et al. observed an interesting difference between the decomposition kinetics of enantiopure (*R*,*R*)-TA and the racemic mixture of (*R*,*R*)- and (*S*,*S*)-TA at saturation coverage (Fig. 2) [42]. As expected, there were no differences between the decomposition kinetics of pure (*R*,*R*)- and (*S*,*S*)-TA, because the Cu(110) surface is achiral.

On the basis of this prior work on surface explosion reactions, Gellman et al. chose to explore the potential for highly enantiospecific decomposition of (R,R)- and (S,S)-TA on naturally chiral Cu(hkl) surfaces [44]. On the Cu(110) surface they were able to show that during heating at 1 K/s, the peak width for TA decomposition can be as



**Fig. 2** CO<sub>2</sub> desorption traces during thermally-induced explosive decomposition of racemic (*rac*)-TA (upper) and (*R*,*R*)-TA (lower) on Cu(110). With increasing initial coverages, the desorption maxima shift to higher temperature, while the peak widths decrease dramatically. Traces obtained from ordered molecular lattices are indicated by down-pointing arrows and the lattice periodicities in matrix notation [43]. The saturation signals are shown as dashed curves. The (4 0, 2 1) phase of the racemate has exactly the same coverage as the (4 0, 2 1) phase of the pure (*R*,*R*)-enantiomer, but 'explodes' at lower temperature (grey area signals). (reproduced with permission from ref. [42], O Wiley & Sons.)

low as  $\sim 0.8$  K. Such observation suggested that on chiral surfaces, even very small differences in the enantiospecific decomposition rate constants should lead to observable differences in the peak temperatures for CO<sub>2</sub> desorption. Figure 3 shows the TPR spectra for  $CO_2$  desorption during decomposition of (R,R)-, (S,S)- and (rac)-TA on the  $Cu(17,5,1)^{R\&S}$  and  $Cu(531)^{R\&S}$  surfaces. The first thing to note is that on all surfaces the decomposition of (R,R)and (S,S)-TA is enantiospecific, exhibiting different peak temperatures on a given surface enantiomer. The origin of these peak temperature differences in chirality is rigorously demonstrated by the fact that the data exhibit diastereomer-ism;  $T_p^{RR/R} = T_p^{SS/S} \neq T_p^{SS/R} = T_p^{RR/S}$ . More importantly, the enantiospecificity of the decomposition rates is extremely high. Figure 4 left shows the (S,S)-TA decomposition rates on  $Cu(643)^{R\&S}$ . The difference in the peak  $CO_2$  desorption temperatures on the two surfaces is 10 K. A simple analysis assuming that the decomposition process was first-order in coverage would suggest that the enantiospecific difference in the decomposition barrier is ~2.8 kJ/mol and that the enantiospecificity of the rates ought to be  $\sim 3.1$  at  $\sim 485$  K. As illustrated in Fig. 4 left, the enantiospecific ratio of the rates reaches a factor of ~50, as a result of the non-linearity of the reaction kinetics. Figure 4 right provides another illustration of the extremely high enantiospecificity of the TA



**Fig. 3** TPRS of (*R*,*R*)-TA, (*S*,*S*)-TA, and (*rac*)-TA decomposition on Cu(17,5,1)<sup>*R&S*</sup> and Cu(531)<sup>*R&S*</sup> surfaces [44]. Left panel: TPRS of (*R*,*R*)- and (*S*,*S*)-TA on Cu(17,5,1)<sup>*R&S*</sup> reveals high enantiospecificity and diastereomerism:  $T_p^{RR/S} = T_p^{SS/R} < T_p^{RR/R} = T_p^{SS/S}$ . Decomposition of the *rac*-TA occurs at the same temperature on both surfaces,  $T_p^{rac/S} = T_p^{rac/R} = T_p^{SS/R}$ . Right panel: TPRS of (*R*,*R*)- and (*S*,*S*)-TA on Cu(531)<sup>*R&S*</sup> reveals high enantiospecificity and diastereomerism, however, the order of stability is reversed from that on Cu(17,5,1)<sup>*R&S*</sup>.  $T_p^{RR/S} = T_p^{SS/R} > T_p^{RR/R} = T_p^{SS/S}$ . Decomposition of the (*rac*)-TA occurs at the same temperature on both surfaces but at the temperature of the more stable adsorbate–surface combination,  $T_p^{rac/S} = T_p^{rac/R} = T_p^{SS/R}$ . (reproduced with permission from ref. [44], © ACS Publ.)

decomposition kinetics on chiral Cu surfaces. Under isothermal conditions at 450 K, (R,R)- and (S,S)-TA decompose with maximal rate on the Cu $(651)^S$  surface after 360 and 478 s, respectively. If one assumed first-order rate constants for the process they would differ by a factor of ~ 1.5 and yet the (S,S)-TA is almost completely consumed before the onset of (R,R)-TA decomposition. Again, the nonlinearity of the decomposition kinetics leads to the extremely high enantiospecificity.

In closing, we note that aspartic acid (Asp, HOOCCH( $NH_2$ )CH<sub>2</sub>COOH) which has a structure similar to that of TA also decomposes via an autocatalytic vacancymediated explosion mechanism on Cu surfaces. Although not as highly enantiospecific as TA decomposition, the nonlinear kinetics of Asp decomposition also lead to very high enantiospecificities on the naturally chiral Cu surfaces [11, 45].

## 4 Adsorption Induced Auto-Amplification of Enantiomeric Excess

Enantiospecific adsorption on chiral surfaces is the basis for chiral separations by chromatography using chiral stationary phases. Such enantiospecific adsorption has been reported on a number of chiral surfaces including metals



**Fig. 4** Left: CO<sub>2</sub> desorption during TPRS of (S,S)-TA on Cu $(643)^{R\&S}$ . The maximum decomposition rate occurs at 486 K on the Cu $(643)^{S}$  surface and at 496 K on the Cu $(643)^{R}$  surface [44]. The enantiospecific ratio of the reaction rates (dashed black) reaches ~ 50 at 484 K. Right: Isothermal TPRS of (R,R)- and (S,S)-TA on Cu $(651)^{S}$  at 450 K. The two enantiomers decompose with maximum rates at

360 and 478 s. The peaks are almost completely resolved from one another indicating extremely high enantiospecificity of the rates. At 430 s the (*R*,*R*)-TA is almost completely decomposed before decomposition of (*S*,*S*)-TA has even begun. (reproduced with permission from ref. [44], @ ACS Publ.)

such as Cu and minerals such as scalenohedral calcite. L-Asp was observed to adsorb preferentially on the (3121) face of calcite, whereas D-Asp adsorbed preferentially on the (2131) face [46]. On Cu(3,1,17)<sup>*R&S*</sup> surfaces D-Asp prefers the *S*-surface while L-Asp prefers the *R*-surface [11]. On achiral surfaces the two enantiomers of a chiral compound should adsorb with no preference; i.e. no enantiospecific difference in their heats of adsorption.

In 1983, Cundy and Crooks observed an interesting phenomenon during the purification of nicotine on an achiral HPLC column [47]. When running a racemic mixture of  $^{14}$ C-*dl*-nicotine through the column it eluted as a single peak. This was not surprising given that the column was achiral and the racemic mixture has no net chirality. However, when they added enantiomerically pure *l*-nicotine (no  $^{14}$ C-label) to the mixture being injected onto the column, the two enantiomers of the <sup>14</sup>C-*dl*-nicotine were eluted at different times; i.e. they had achieved enantiomer separation using an achiral column. They attributed this phenomenon to enantiospecific aggregation of enantiomers in the column (either in the stationary or moving phase) and the differential transport of dl versus dd (or ll) aggregates down the column. Since then there have been numerous corroborating observations and studies of the phenomenon, now called 'enantiomer selfdisproportionation' [48, 49].

Recent measurements of the equilibrium adsorption of enantiomer mixtures onto chiral and achiral single crystalline Cu surfaces have demonstrated that enantiomer aggregation can lead to non-linear effects in adsorption and even to local amplification of enantiomeric excess on achiral surfaces (Fig. 5) [9–11, 50, 51]. By co-adsorbing mixtures of amino acid enantiomers onto surfaces under conditions that allow equilibrium adsorption, it has been possible to quantify the ratio of adsorbed enantiomers and thereby the surface enantiomeric excess,  $ee_s$ , versus the gas phase enantiomeric excess,  $ee_g$ . Not too surprisingly, exposure of a racemic mixture of D- and L-Asp in the gas phase,  $ee_g = 0$ , to chiral Cu(3,1,17)<sup>*R&S*</sup> surfaces results in the preferential enantiospecific adsorption of one enantiomer over the other,  $ee_s \neq 0[11]$ . In contrast, exposure of a racemic mixture of *DL*-Asp,  $ee_g = 0$ , to the achiral Cu(111) and Cu(100) surfaces simply results in the adsorption of a racemic mixture,  $ee_s = 0$  [11, 51]. The surprising observation is that, exposure of the achiral Cu(111) surface to a non-racemic mixture in the gas phase,  $ee_g \neq 0$ , results an adsorbed mixture with an even higher enantiomeric excess,  $|ee_s| > |ee_g|$ . This is not a trivial effect; exposure of a mix-

ture with a 2:1 ratio of D- to L-Asp in the gas phase results in the equilibrium adsorption of a mixture with a 16:1 ratio of D- to L-Asp. Figure 5 left shows a plot of the dependence of  $ee_s$  on  $ee_g$  for adsorption of mixtures of D- and L-Asp onto Cu(111) at 450 K. Because the surface is achiral it must be the case that  $ee_s = 0$  when  $ee_g = 0$ , as observed. However, the curve for  $ee_s$  versus  $ee_g$  is non-linear, in spite of the fact that all of the equilibrium constants for the adsorption process must be non-enantiospecific,  $K_{ads}^D = K_{ads}^L$ . The observed behavior demonstrates autoamplification of  $ee_s$  on the surface, i.e.  $|ee_s| > |ee_g|$ , in spite

of the fact that the surface is achiral. This behavior must originate with some form of non-linear process occurring during adsorption. The simple first-order competitive Langmuir adsorption isotherm that would commonly be





**Fig.5** Left: Equilibrium isotherm representing the enantiomeric excess of the surface,  $ee_s$ , versus the enantiomeric excess in the gas phase,  $ee_g$ , during exposure of the achiral Cu(111) surface to mixtures of D- and L-Asp. First-order competitive adsorption via a Langmuir isotherm would predict  $ee_s = ee_g$ . Right: Adsorption of enantiomers

in the form of homochiral clusters or aggregates of *n* monomers predicts the non-linear isotherm observed. The solid line on the left is for n=10. Note that, because the surface is achiral the equilibrium constants are not enantiospecific; i.e.  $K_{ads}^D = K_{ads}^L$  and  $K_{agg}^D = K_{agg}^L$  [51]

used to describe co-adsorption of two adsorbates fails to capture this type of phenomenon.

A simple modification of the competitive Langmuir adsorption isotherm can predict the observed dependence of  $ee_s$  on  $ee_g$  for D- and L-Asp adsorption onto Cu(111) [50, 51]. The right panel of Fig. 5 illustrates an adsorption model in which monomers of D- and L-Asp form homochiral aggregates once adsorbed on the surface. Evaluation of this adsorption model yields the solid line in Fig. 5 left for aggregates of n = 10 monomers, for a fairly modest aggregation energy of  $\Delta G_{agg} = 6$  kJ/mol of monomer. It is important to note that this behavior leads to the non-linear auto-amplification of *ee*, in spite of the fact that the underlying equilibrium constants for adsorption and aggregation are non-enantiospecific; i.e.  $K_{ads}^D = K_{ads}^L$  and  $K_{agg}^D = K_{agg}^L$ . It is also important to note that the observed behavior stipulates that the aggregation is predominantly homochiral rather than heterochiral. Heterochiral aggregation would result in suppression of  $ee_s$  with respect to  $ee_g$  or, in other words  $|ee_s| < |ee_g|.$ 

## 5 Sergeant-and-Soldiers Principle and When the Majority Rules

Helicity in molecules and polymers is clearly a manifestation of chirality and is abundant in the biomolecular world. Long strands of achiral helical polymers tend to exhibit both signs of helicity accompanied with helix inversions in the chain. In a series of elegant experiments, Mark Green et al. studied the induction of homochirality by introduction of chiral bias in the form of chiral side chains [52]. The equal probability for left- and right-handed helicity in polyisocyanate polymers with achiral side chains make them optically inactive. A few percent of homochiral side chains ('sergeants'), however, causes a large circular dichroism due to single helicity in all strands. The small chirality bias from the side chains, causes a small steric preference for the sign of helicity of a turn in the strand ('soldiers'), and as a result the energetically less favored helix inversions team up in a cooperative manner to induce homochirality in the entire system [53]. A similar outcome, coined 'majority rule', was achieved when a ratio of 49–51% of left- and right-handed chiral side chains were used; the entire strand had the helicity associated with the chirality of the majority side chain [54]. Both non-linear phenomena, the 'sergeant-and-soldiers' principle and the 'majority rule' can be also be at work in non-covalently-interacting supramolecular self-assemblies of disk-shaped molecules [55, 56].

The sergeant-and-soldiers (S&S) effects can be also observed in two-dimensional (2D) lattices on surfaces [57]. A common observation of mirror symmetry breaking in surface science is the creation of extended chiral adsorbate lattice structures, even when the adsorbate is achiral. An example is succinic acid (SU, HOOC-CH<sub>2</sub>-CH<sub>2</sub>-COOH) on Cu(110), where both enantiomorphous domains were observed with low energy electron diffraction (LEED) and scanning tunneling microscopy (STM) [58]. However, mixing only 2% of either enantiomer of chiral tartaric acid into the monolayer induced homochirality, i.e. only one enantiomorph of the two mirror domains was observed on the entire surface [59]. The same effect has been shown for achiral (R,S)-TA as soldiers and chiral TA as sergeants on Cu(110) [60]. By strongly interacting through both carboxyl groups with the metallic substrate, SU and (R,S)-TA create a chiral footprint [61], most-likely causing a chiral reconstruction in the top layer of the Cu(110) surface. The chiral footprint of TA-enantiomers on Cu(110) has been experimentally

determined with X-ray photoelectron diffraction (XPD) [62], and reconstructions have been identified by STM for other dicarboxylic acids on the same substrate [63–65]. Hence a 'through-substrate-chiral-footprint' scenario seems very plausible for this kind of 2D S&S chiral amplification. Note that S&S cooperative effects have also been reported at the liquid–solid interface [66, 67], even induced by chiral solvents [68].

A 2D equivalent of the 'majority rule' mechanism has also been established previously. When racemic mixtures of chiral molecules are adsorbed on a surface, two principle scenarios are possible. Either the enantiomers separate laterally, forming a conglomerate of homochiral domains, or the two enantiomers aggregate into heterochiral pairs and crystallize into a racemate lattice. But if the relative alignment of the two enantiomers in the racemate lattice on the surface breaks mirror symmetry, such a pair can be considered a chiral entity itself. Which means that on a covalently bound molecular level the system is heterochiral, but on the supramolecular level the system can become homochiral. However, on an achiral substrate two enantiomorphous alignments of pairs must exist and both mirror domains will be observed. But any ee, imposes a chiral bias that favors one enantiomorphous dimer alignment and, therefore, only one of the two mirror domains can exist due to enantioselective interactions at domain boundaries.

The racemic mixture of heptahelicene ([7]H;  $C_{30}H_{18}$ ) on Cu(111) represents exactly such a system. The (M)- and (P)enantiomers ((M) for minus; (P) for plus) assemble into zigzag rows with (M)/(P)-pairs aligned into two enantiomorphs, building up left- and right-handed mirror domains (Fig. 6) [69]. Enantiomeric excess of just 7% leads then to the situation in which only a single mirror domain type is observed [69, 70]. Although still close to a racemic state at the molecular level, homochirality is imparted globally. Sufficient excess of (M)-[7]H leads exclusively to  $\lambda$ -domains (Fig. 6b), and an excess of (P)-[7]H exclusively to  $\rho$ -domains. The long-range ordered domains are still racemic and the excess is located outside in less ordered areas. These less ordered areas contain homochiral assembly motifs, which were previously also observed for the pure enantiomers [71]. That is, chiral pinwheel structures formed in the monolayers of pure enantiomers are also found in the excess regions (Fig. 6b). Molecular modeling calculations show that (i) an  $ee_s$  cannot exist within a  $\lambda$  or  $\rho$  domain, that (ii) mirror domain boundaries between  $\lambda$  and  $\rho$  domains impose a higher energy situation, and (iii) confirm a stereospecific influence onto the alignment of the entire domain from the outside. There is strong enantioselectivity for formation of one domain type at close packing with  $ee_s$  at the outside (Fig. 6c, d). Another factor is that the energetically less favored mirror domain boundaries are easily avoided. Because of the non-covalent



**Fig. 6 a** STM images (10 nm×10 nm) of two enantiomorphous domains ( $\lambda$ ,  $\rho$ ) formed of alternating (*M*)- and (*P*)-[7]H enantiomers in zigzag rows (superimposed with molecular models). The inset shows ball-and-stick models of the enantiomers. **b** Excess of (*M*)-[7] H creates exclusively  $\lambda$  domain assembly. Pinwheel-motifs of small clusters (green), which are observed near  $\lambda$  domain boundaries, are

assigned as homochiral (*M*)-[7]H structures. The insets show the pinwheel motifs observed in enantiopure monolayers. **c** Sketch of molecular modeling simulations of five enantiomers densely packed near a  $\lambda$  domain boundary with decreasing area. **d** This result of the simulations shows that (*M*)-[7]H can be accommodated at higher density before strong intermolecular repulsion arises

binding in a heterochiral pair, its handedness can be easily switched between enantiomorphs. Consequently, a small  $ee_s$  will be amplified into a homochiral alignment of all heterochiral (M)/(P)-pairs.

So far, the examples presented have allowed an easy switching between enantiomorphous states. Although the [7]H molecules themselves did not switch their handedness, the (M)/(P)dimer did. The backbone of adsorbed succinic acid could be enantio-interconverted at the molecular level because there is no intrinsic preference for either enantiomeric state. But what if a chiral molecule does not form a racemic lattice with both enantiomers, but a 2D conglomerate with non-interconvertible units? One would expect that ee, leads to a corresponding ratio of domain areas. Such a state was indeed observed for mixtures of (R)- and (S)-phenylalanine on Cu(110) [72]. Racemic tartaric acid forms a 2D conglomerate at a coverage of 2/3 of the saturated monolayer [42]. At the relatively small ee, of 20%, however, the domains of the minority completely disappear [73]. But that does not mean that the majority grows at the expense of the minority. Even at  $ee_s = 0$ , STM shows, in addition to the homochiral (12, -82) and (1-2, 82) domains of the pure enantiomers, areas with short-range order, but with a preferential alignment parallel to the high-symmetry direction of the Cu(110) substrate. Note, that with increasing coverage, the (rac)-TA/Cu(110) system undergoes a transition from a conglomerate to a (40, 21) racemate crystal system with adlattice vectors perfectly aligned to the Cu substrate vectors (see also Fig. 2) [42]. At  $ee_s = 0$  a substantial fraction of the molecules goes into an unbalanced mixture with low ordering [74]. That a chiral impurity in the form of the enantiomer destroys long-range order has also been shown for [7]H on Cu(111) at  $ee_s > 90\%$  [70]. As a consequence of increasing  $ee_s$ , the homochiral domains of the minority will be increasingly dissolved into the unbalanced-mix area. Interestingly, exactly the same phenomenon has been observed when (rac)-TA was co-adsorbed with either enantiomer of malic acid (MA, HOOC-CH2-CH(OH)-COOH) [32, 74]. (R)-MA made (S,S)domains disappear, while (S)-MA suppressed the (1 2, -8 2)(R,R)-domains. Strong preferential hydrogen bond interactions between the different species were suggested in this case, but the same effect was also observed for mixtures of (M)-[7]H and the racemate of its isomer dibenzopentahelicene (db[5] H) [75]. Although the examples presented in this section lead to a single enantiomorphous state, they do not include any amplification. They resemble only enantioselective annihilation by an external chiral influence. They are discussed here in order to highlight processes that seem to fall into the category of chiral amplification but are based on different mechanisms.

# 6 Amplification of Chirality in Crystalline Solids

In 1898, Kipping and Pope performed crystallization experiments with sodium chlorate with and without chiral bias [76]. Although achiral at the molecular level, NaClO<sub>4</sub> forms enantiomorphous crystals that can be distinguished by their mirror-breaking shape, but more conveniently by using a polarization microscope. After numerous experiments, they could not identify any significant excess of handedness, unless chiral substances were added. Kondepudi et al. confirmed this observation for unstirred crystallization from supersaturated solutions [77]. When the solution was stirred, however, they observed exclusively single enantiomorphism in the solid state. Either handedness was formed with a 50% chance, but each single experiment yielded homochirality. An explanation was given later by McBride and Carter, who filmed the process and identified secondary nucleation as mechanism [78]. Primary nucleation at certain supersaturation is a slow process, but when a nucleus ('Adam crystal') gets hit by a mechanical stirrer, it shatters into many small nuclei of the same kind leading to fast crystallization of crystals exhibiting identical enantiomorphism. At the same time the supersaturation drops quickly, with the consequence that the critical radius supporting further growth is largely increased, not allowing the other enantiomorph to crystallize. That seeding with crystals of an enantiomer favors nucleation and growth of the same kind from supersaturated solution had already been mentioned for tartrate salts by Pasteur's former student Gernez in 1867 [79].

A stunning observation of mirror-symmetry breaking was reported by Viedma in 2005 [80]. By grinding enantiomorphous crystals of sodium chlorate in contact with a saturated solution of this achiral compound, the precipitate turned into an ensemble of homochiral NaClO<sub>4</sub> crystallites (Fig. 7). Quickly, this method became extended to intrinsically chiral



**Fig. 7** Homochirality in the solid phase by attrition. A slurry containing both enantiomorphs of crystalline  $NaClO_3$  (orange and blue polygons) turns homochiral by stirring under simultaneous abrasion of crystallites. Glass beads are indicated as small grey spheres

compounds with a low racemization barrier in solution [81]. Initially the mechanism was heavily debated and variations of Oswald ripening or selective surface autocatalysis mechanism were proposed [81, 82].

The classical picture of crystal growth from the melt or solution discusses particle-by-particle (ions, atoms or molecules) attachment after the nucleus is viable to grow (Gibbs-Thomson effect and Oswald ripening). However, there were early observations that questioned Ostwald's supersaturation and growth picture [83]. By considering a new kind of crystal growth McBride et al. could finally explain satisfactorily this symmetry breaking by Viedma ripening [84, 85]. In classical Ostwald ripening only sufficiently large nuclei are allowed to grow (retaining their handedness). Constantly chipping off crystallites by grinding will keep crystals small and suppresses further growth by favoring dissolution. But when crystallites coalesce selectively, that is, only fragments of the same handedness will get attached to a larger particle, the majority will successively grow while the minority tends to go into solution. Indeed, enantioselective and stereoselective attachment of crystallites as mechanism of crystal growth has been shown with dyed crystals and directly with transmission electron microscopy, respectively [86-88]. As in the Frank model, a small enantiomeric imbalance will be amplified until only one handedness prevails in the solid state. Because the solution of NaClO<sub>3</sub> is achiral there is no *ee* in the solution phase. For intrinsically chiral systems, deracemization in the solid state via Viedma ripening requires crystallization as a conglomerate and a low inversion barrier between the enantiomers such that a racemic solution state is maintained [85]. While deracemization in Viedma ripening happens at the scale of hundreds of nanometers, there are hints that the emergence of homochirality may also occur at a much smaller scale at the level of subcritical clusters. Supersaturated boiling NaClO<sub>3</sub> solutions yielded homochiral solids in very fast crystallization events [47, 89]. Liquid samples taken at different locations in the supersaturated solution before crystallization showed a clear correlation in handedness [90].

There are more examples of chiroselective (self)replication and polymerization in oligo- and macromolecular systems as well as mirror symmetry breaking due to selective interactions with crystal surfaces. Good reviews can be found in [91, 92].

### 7 Conclusions

The procreation of life is the most obvious example of a chiral autocatalytic process by which the homochiral molecular basis of life is amplified. As summarized, herein, there are also many abiotic processes with the characteristic of autocatalysis and the nonlinear dependence on concentration that can lead to a high degree of symmetry breaking in chiral molecular processing. Given the intrinsically low enantiospecificities of chiral reaction energetics, such non-linear processes offer routes to achieving the high enantioselectivities critical to the successful production of enantiomerically pure compounds for pharmaceutical needs. The fact that these types of non-linear phenomena can be observed on surfaces suggests that chiral surfaces can be developed as highly enantioselective catalysts.

Homochirality is an imperative manifestation of life. Several interstellar symmetry-breaking scenarios, causing an intrinsic bias in molecular chirality, have been proposed. The other possibility is that homochirality evolved from a racemic state in the prebiotic soup. But how (if at all) it propagated into homochiral systems is still not understood. We have reviewed here a few abiotic autocatalytic enantioselective processes that have the potential to have led to the homochiral state even before life forms were 'created'. But how life evolved from homochiral supramolecular systems saying it with the words of the Nobel laureate Vladimir Prelog—belongs to the realm of molecular theology.

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