THE CONCEPT OF RACEMATES AND THE SOAI-REACTION

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Abstract

The traditional concept of racemates means an exactly 1:1 mixture of two enantiomeric molecules. Modern analytical and catalytic/preparative discoveries, first of all the Soai-reaction, make necessary a re-evaluation of this concept. The most important aspect of such a revision is the definition of the amount of an excess of one or of the other enantiomer, originating from statistical fluctuation, which can still be „tolerated" when a substance is defined as *racemate*. The present paper discusses the statistical view of racemates and some related problems.

Keyword

Chirality; Racemates; Chiral Autocatalysis; Enantiomers, statistics of; Weak nuclear forces, asymmetry of

1. Mirror Images

The relation between an object and its mirror image [1] is an exciting challenge for Humanity – most probably since very ancient times. While in the case of object/mirrored image the first could be physically "touched" and the second not, the relation between "enantiomeric" object pairs as, for example, a pair of gloves or left and right handed screws (Fig. 1 [2]) is much more problematic. In the case of such mirror image object pairs the correlation of the two objects is highly dependent on the exactness and resolution of the observation (and its technology). These factors are critical to the decision whether the two objects *are exact "mirror copies" of each other* or not? Progress in the observation technology requires, time-to-time the revision of such statements. This paper will discuss the need for revision of such a concept, that of the *molecular racemates* in chemistry.

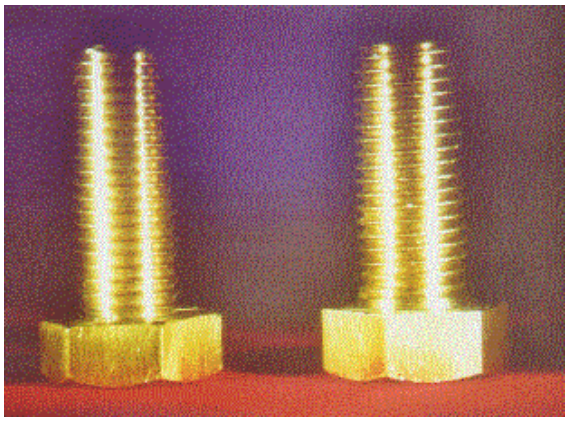


Figure 1.
Right- and left-handed screws [2]

2. Molecular/Atomic Chemistry

Preparative, analytical or structural statements of chemistry traditionally refer to average behavior of a very large number of molecules [3]. Typical

"chemical sizes" are *mol*, its thousandth (*mmol*) or millionth (*μmol*) parts. While in usual chemical thinking (receipts, analyses, etc.) *μmol* is regarded as a fairly small quantity, it is only rarely taken into consideration that even also this order of magnitude means the average or "majority" behavior of a huge number of molecules, ions, atoms. One *mol*, as it is well known is 6.022×10^{23} pieces of particles, its millionth is still a very-very large number: 6.022×10^{17} (this can be sensed considering the fact that this number is approximately hundred-million times the present number of Humanity).

Development of various chemical analytical, preparative, instrumental, etc. techniques towards very small sizes was very rapid and efficient in the past few years (Table 1).

Frontier results [4] of these "sub-microchemical" tendencies frequently refer to such a small number of molecules, which by no means could be viewed using the "laws of the great numbers". These trends of chemical miniaturization open new possibilities but also new problems in chemistry; an example of this is the need for the re-evaluation of the concept of racemates – a concept which did not awake too much intellectual excitement in the last century. It is the principal goal of the present paper to outline some considerations and experimental results concerning these problems, but first of all an attempt will be made at the exact definition of the category of *racemates*.

3. Racemates

The formation of racemates is due to the fact that "when a center of asymmetry is formed in achiral environment the probabilities of formation of the two isomers [enantiomers] are exactly equal. In the resulting equimolar mixture the optical activities of the two forms are compensating each other (intermolecular compensation): and consequently optically inactive, so-called *racemic modification* is formed". (This citation was taken from one of the best textbooks of organic chemistry known to the Authors [5].) Historically the concept of racemates is a product of Pasteur's studies regarding the structure of *dl*-tartaric acid (racemic acid, racemus (lat.) =

Table 1 Number of sub-microchemical publications* in the web-site SciFinder Scholar of the American Chemical Society (A: on March 19, 2004; B: on April 11, 2005)

Order of magnitude	Number of molecules	Number of publications	
		A	B
femtomol, 10^{-15} mol	$6x10^{8}$	457	1805
attomol, 10^{-18} mol	$6x10^{5}$	222	709
zeptomol, 10^{-21} mol	$6x10^{2}$	40	144
yoctomol, 10^{-24} mol	0.6^{**}	15	17
single molecules	1	4	31
single atoms	1	8	119
visualization of molecules	1	10	21
visualization of atoms	1	7	11

* The original meaning of "microchemical" would be *μmol*-chemistry.
** One *yoctomol* obviously can not be interpreted chemically, since one molecule is ~1.7 ymol. In these publications the sensitivity threshold is a few dozens or a few hundreds of molecules (corresponding to few times ten or few times hundred yoctomol).

cluster) [6], it was Pasteur who recognized, that this acid is a 1:1 mixture of *d*- and *l*-tartaric acid (*racemate*). Macroscopically, the most characteristic feature of racemates is the absence of optical activity, which, however, is dependent on the sensitivity of the measurement.

The actual problems with racemates start to emerge, when the expressions "equimolar mixture", "1:1 mixture" or "probability of formation" (in the above cited definition) are analyzed somewhat more acutely. These problems will be discussed in the following section of the present paper.

4. Statistical Description of Racemates

Enantiomers are *exactly* of the same structure, with the only difference that they are *specular images* of each other. As a consequence of this circumstance all chemical (bonding) and "supramolecular" (attractive and repulsive) intramolecular interactions are exactly equal in the two isomers, consequently also their energy content will be equal, which again causes that the probability of their formation will be identical (this picture today is not *exactly true*, as it will be discussed later, but for the present argumentation it could be accepted as a very good approximation). If, then, a chiral substance is prepared (formed) from achiral precursor, without any chiral additive or chiral physical influence, the *chances* of the formation of one or the other form (with opposed chirality) are equal, as, for example, it is in the case of tossing a coin, resulting one or other side of the coin becoming the "upper" or the "lower". *Equal chance*, however, does not mean, that numbers of *the results* will be *exactly equal* [7]. This important point in the context of enantiomers was clearly analyzed by Pearson [8] as early as around the end of the XIXth century. This interesting aspect of chirality emerges periodically again and again in the literature of the last Century and even also very recently [9-17].

This statistical view of the racemates leads to a number of interesting consequences.

One of these is obvious, but only very rarely mentioned [9]: *true racemate* is only possible when the mixture is composed of an *even number* of molecules, while with an *odd number* of particles at least one molecule enantiomeric excess *must be* present, it follows from this that the *chance* of the formation of a "true" racemate cannot go beyond the upper limit of 50%. When this distinction was mentioned first, around the beginning of the XXth century, it might have been considered as a hair-splitting speculation but, today, when the forefront of sub-microchemical research is reporting on *yoctomol-level* observations (Table 1) it should be seriously considered.

The statistical ("tossing") nature of the formation of racemates, however, permits much higher enantiomeric excesses[i] than one single molecule. The deviations from the *exactly* 50-50% distribution cause (or more exactly: *may* cause) significant enantiomeric excesses, especially in the case of low particle number (n~<50) systems.

Mathematical treatment of these problems is one of the simplest cases of probability theory [7]. It can be formulated as follows. If the (enantiomeric) molecules are formed independently of each other (no chiral induction), with equal probability (*P*) of the occurrence of the $n = d + l$ distribution can be calculated according to the binomial distribution [7]:

$$P\,(n=d+l) = \left(\frac{n}{d}\right) * \left(\frac{1}{2}\right)^{d} * \left(\frac{1}{2}\right)^{l} = \frac{n!}{d!*l!*2^{n}}$$

First of all, it should be stressed that the formation of the *first chiral molecule* (from achiral precursor) *must* yield 100% e.e., even if we cannot predict *which enantiomer* will be formed as first. Statistics "awakes" only at the formation of the *second chiral molecule* [7c].

[i] e.e. = $[(d-l)/(d+l)]*100$ or $[(l-d)/(d+l)]*100$ for $d>l$ or $l>d$ respectively.

All possible distributions for the case of 10 molecules together with some selected examples with greater numbers are shown in Table 2.

If the number of molecules is n>20 the distribution can be described with the standard normal distribution, then if the binomial probability variable d can take the d = 1,2, … n values the expectable value (m) and the standard deviation (σ) will be:

$$m = \frac{n}{2} \qquad \sigma = \frac{\sqrt{n}}{2}$$

Mills [10] introduced for non-equal molecule numbers ($d \neq l$) with asymmetric distribution, that minimal $e.e._{1/2}$ value, above which a higher e.e. takes place with 50% probability. This is:

$$e.e._{1/2} = \frac{|d-l|}{n}$$

Table 2
Probability (P) of some distributions in small samples of two kinds of enantiomeric molecules (d and l).

Distribution	**(n = *d*+*l*)**	**Order of magnitude**	**P(n = *d*+*l*)**
Equal	(10=5+5)	*yoctomol*	24.6 %
2-molecule more from one kind	(6+4) or (4+6)		41.0 %
4-molecule more from one kind	(7+3) or (3+7)		23.4 %
6-molecule more from one kind	(8+2) or(2+8)		8.8 %
8-molecule more from one kind	(9+1) or (1+9)		2.0%
All molecule of the same kind	(10+0) or (0+10)		0.2%
Total			100.0 %
Equal	(100=50+50)	*yoctomol*	7.96 %
	(1000=500+500)	*zeptomol*	2.52 %
	(10000=5000+5000)	*attomol*	0.8%
	(100000=50000+50000)		0.25%
	10^8	*femtomol*	0.008%
	10^{20}	*millimol*	$8\ 10^{-9}$%
All molecule of the same kind	(100+0) or (0+100)	*yoctomol*	$1.58\ 10^{-28}$%
	(1000+0) or (0+1000)	*zeptomol*	$1.87\ 10^{-299}$%
	(10000+0) or (0+10000)	*attomol*	10^{-3008}%
	(100000+0) or (0+100000)		10^{-30101}%

This value corresponds to the sum of the "lower" and "higher" quarters of the area under the normal distribution curve (Gauss-distribution).

The standard ($m = 0$, $\sigma = 1$) normal distribution is tabulated in usual mathematical handbooks. The standardized variable (t) is:

$$t = \frac{d - m}{\sigma} = \frac{d - \frac{n}{2}}{\frac{\sqrt{n}}{2}}$$

The points corresponding to 75% and to 25% result t = 0.675 and -0.675 respectively, the difference between these points can be transformed to the e.e. scale, as e.e. = (d-l)/(d+l) or e.e. = (l-d)/(d+l) this yields for $e.e._{1/2} = \frac{0.675}{\sqrt{n}}$, as suggested by Mills [10]. Some characteristic enantiomer excess ($e.e._{1/2}$) values are tabulated in Table 3.

The data in Tables 2 and 3 allow some interesting qualitative statements:

(a) Systems with a low number of particles ($n \sim< 20$) allow the statistical evolution of relatively high enantiomer excesses with not in the least negligible probabilies particularly on the *yoctomol* or *zeptomol* level.

(b) Even at systems with large number of molecules there is a significant probability of the development of mixtures containing *yoctomol* or *zeptomol* quantities of excess from one of the enantiomers.

(c) It can not be excluded that some sporadic observations of unexpectedly high and non-reproducible enantiomeric excesses might be due not to artifacts or even fraud but to fortunate (?) accidental occurrence of a low-probability, high-e.e. "event". A number of such reports elicited usually severe criticism, but – as it was pointed out recently by Kurt Mislow [17] – some of such reports may be the result of a "high-amplitude", almost singular event. (Mislow cited also a remarkable candidate for such an observation [18].)

The above listed reflections clearly indicate, that the content of the word "racemate" should be re-considered. First of all in the future not only the minimum enantiomeric purity of "pure" enantiomeric compounds, but *also the maximum excess enantiomeric content of racemates* must be given in commercial specifications or in scientific descriptions (eventually together with the indication of the method of analysis, e.g. optical rotation, ORD/CD, chiral chromatography, NMR, etc.). We believe the experimental results and theoretical ideas, which will be described later in this paper, are providing additional arguments for the necessity of this recommendation, before this, however, we would like to draw attention to some interesting conceptual features related to racemates.

According to limits of the measurement, a sample may contain some excess of one of the enantiomers which can not be detected. Such samples were called "cryptochiral" [17], which we feel

Table 3
Number of molecules (n) and the statistical enantiomeric excesses with 50% probability ($e.e._{½}$) according to Mills.[10]

n	**$e.e._{½}$·100 (%)**
100	7
1000	2
10^4	0.7
10^5	0.2
…	…
10^{2k}	$7\times10^{-(k-1)}$
10^{2k+1}	$2\times10^{-(k-1)}$
…	…

somewhat misleading, a numerical specification of the limits of measurement appears to us more appropriate.

Another problem is that of the *meso*-isomers. *Meso*-compounds contain (at least) two centers of asymmetry (on identical atoms), where the same groups are connected to these centers but these groups are distributed in opposite configurations. Thus these compounds can be viewed as "intramolecular racemates". Considering this fact, it will be clear that in *meso*- compounds to *all* centers of chirality with (let us say) S configuration in *all cases exactly* one R center is belonging: we could say that these compounds can be considered, even according to the highest demands, as *standards* of the *racemates*, supposed, that the sample of the *meso*-compound is sufficiently pure. Maybe, that in the future, some sensitive parameters which cannot be exactly studied at racemates because of the statistical fluctuations, could be advantageously investigated with *meso*-compounds.

An additional conceptual matter related to racemates is the question of the "absolute enantioselective synthesis".

In the last century, also even recently, there was some uncertainty about the definition of this concept [17, 19-25]. We believe, today the most exact definition can be formulated as follows: absolute enantioselective synthesis is such chemical reaction which starts from achiral compounds and proceeds *without any chiral additive* or *without any asymmetric physical field*. If this reaction yields a chiral product with more or less excess of one of its enantiomers it can be called *absolute enantioselective synthesis* (we have taken this definition essentially from the excellent, recent review of Mislow [17]). This definition, however, should be supplemented with some considerations on the basis of the above described facts and their consequences.

(i) First of all 50% of the "non-enantioselective" syntheses should be regarded as "absolute enantioselective synthesis" (AES), since these lead to an odd number of molecules and therefore the product *must* contain 1 molecule (~1.7 *yoctomol*!) excess from one of the enantiomers.

(ii) Regarding the (more or less) enantiomeric excess, to be produced in the AES, it seems to be recommendable to take reservations about the reproducibility (and its allowable dispersion). That enantiomeric excess could be "accepted" which *is emerging* trustworthily from the "background noise" of the expected statistical fluctuation (which is, however, dependent on the size of the experiment).

(iii) The absence of "chiral additives" is getting a major problem approximately below the *femtomol* level. Such chiral "contaminants" as microorganisms on the surface of dust particles would need at least such sophisticated instrumentation, which is used by NASA in an attempt to avoid "exportation" of terrestrial microorganisms by space vehicles. Here the problem to be solved, is even more complicated: while an efficient sterilization (e.g. by radiation) could *kill all microorganisms*, this operation however, leaves more-less intact the *chirality* of their organic component molecules. The presence of such chiral contaminants was suspected as one of the possible reasons of unexpected enantioselectivities in a paper published

in a highly competent Journal [26] quite recently. One could ask that general question, whether it is possible at all to exclude all chiral "contaminants" under terrestrial conditions beyond *pico*- or *femtomol* level? This again should be seriously weighed when extraterrestrial samples are (or will be) analyzed for chirality.

(iv) Exclusion of asymmetric physical influences is easy to a certain level, if illumination by polarized light is not applied or the magnetic stirrer is operated in both directions, etc. Beyond this, however, it is impossible to exclude one chiral influence, which is the asymmetry of the *weak nuclear forces*, which is present in all non-H atoms. (This influence will be discussed later in this paper.)

The statistical way of looking at racemates has two additional consequences, which – according to the best of our knowledge – have almost no literature precedents.

The first of these points is coming from the fact, that the majority of natural chemical elements is composed of isotopes. The chemical effect of isotopes is usually not very significant, even if, for example the biological fractionation of ^{13}C is a very important signature of living organisms [27]. The most extensive isotope effect is observed in the H/D relation (because of the large mass difference). Chirality due to isotopic (especially H/D) substitution sometimes gives rise to well-observable effects, as for example *chiral induction*. It can be easily calculated that the mono-α-D-substituted "isotopomer" of diethyl ether (supposing 0.156% natural abundance of D [28]) is present in each *mol* of Et_2O in 62.4 *mmol* quantity. In this quantity, the statistically expectable *excess of one of the enantiomers* is 8.1 *pmol* (8100 *fmol*) which is a large quantity with respect to the orders of magnitude shown in Table 1. Thus, if a sensitive system is studied, it is not "necessary" to be present a "biological contamination" for getting (systematic) chiral induction, it is enough that diethyl ether is used as solvent (large excess!) and in the laboratory the solvent is taken from the *same* 5-l flask, its original (statistical) isotope-chirality cannot be eliminated by no usual purification technique.

The same phenomenon may occur also with other compounds with stereochemical consequences, which could be difficultly neglected, thus *e.g.* the *mono-α-deuterated glycine becomes chiral* (two enantiomers), while mono-β-deuterated alanine and several other natural amino acids generate *diastereomers*, which in statistically "favorable" cases might reach significant excess levels.

It should be pointed out that the isotope-derived kind of statistical chirality has never been experimentally observed (or – at least – reported) yet.

A principally similar, but physically very different phenomenon can be deduced from the relative spin populations of H atoms in some molecules. It is known since longer time that H_2 molecules with parallel (*ortho*-) and opposite (*para*-) nuclear spins can be separated also preparatively [30a-d]. Recently Russian scientists succeeded in separation (enrichment) *ortho*- and *para*-water, which were then identified by spectroscopic methods [30e-g]. In course of these studies Tikhonov and Volkov [30e] noticed, that the *ortho/para* conversion of water is much slower (~10^6 times!) than it could be expected on the basis of its proton exchange rate [31]. This observation (which should still be explained) is relevant to the above outlined problems in two ways. First, as it has been pointed out recently by Shinitzky et al. [32], the two kinds of water molecules could provide a chiral microenvironment for solutes in aqueous solutions. Furthermore, if the *ortho/para*-

(spin)-isomers of water possess a well-defined identity enabling experimental grasping of these species, it could be rightfully expected, that other light elements (E) would form enantiomers of their $R^1R^2EH_2$ ($R^1 \neq R^2$, any non-H atom or group) compounds could yield chiral structures in their *para*-form. (We suggest these spin-isomers could be called *spinomers* for commodity.) In this way "α-*para*-glycine" becomes chiral enantiomer (racemate?) and compounds like alanine or phenylalanine and other $RCH_2CH(NH_2)COOH$ compounds generate diastereomeric "spinomers". About the expectable lifetime, chiral "inductive power", enantiomer distribution and several other important parameters we could make presently only a guess, or even not that without engrossed theoretical and experimental work. Such efforts would be very actual since this effect may have an important influence on the stereochemistry, reactivity or biological role for the very reason that H (procium) makes out an overwhelming majority of the hydrogen isotopes in its compounds.

Surprisingly, the interesting phenomenon of nuclear spin isomerism ("spinomerism") was only scarcely studied at small molecules other than H_2 [33]. The most interesting one from these sporadic studies is the observation of the spin-isomers of formaldehyde [33c,f]. *Ortho*- and *para*- "spinomers" of formaldehyde may play a certain role in its oligomerization, the so-called "formose" reaction, which is believed to be of some importance in life-precursor (prebiotic) chemistry [14, 23].

5. Racemates and Nuclear Physics

The asymmetry of the weak nuclear forces was one of the most interesting discoveries of modern physics, about 40 years ago [34]. A consequence of this is that all non-H atoms are *eo ipso* chiral which could be demonstrated also experimentally for a few heavier atoms [35]. One of the consequences of this effect is, that enantiomers of chiral compounds, which earlier were believed to be *exactly* of the same energy, should be *energetically* slightly *different*: this difference appears to be of the order of $10^{-14} \div 10^{-13}$ J/mol, according to theoretical calculations [36], but experimental verification of these results is still lacking. The enantiomer excess generated by this, so-called, nuclear parity violating effect, could be estimated as being of *femtomol/attomol* order of magnitude [26,36,37], which attracted considerable attention in the last two decades [14,23,37-39]. This slight excess could be observed experimentally only with considerable difficulty, one of the most ingenious approaches uses crystallization of racemates of chiral transition metal complexes as probe [40].

The asymmetry of the weak nuclear forces has also another consequence for racemates. This nuclear parity violation (NPV) effect causes that racemates could *not* be regarded *exactly* as racemates, not even in ideal case (that is: even number of molecules, exactly 1:1 R/S ratio) because of the interaction of the asymmetric nuclear forces (which have the *same direction* in both enantiomers) with the chiral electron orbitals (which are oriented in *opposite directions*) in the two enantiomers. As a consequence of this situation the enantiomers become energetically (slightly) different, which should affect also the bonding distances, angles, etc. – but such differences have not yet been detected experimentally in chemical reactions.

Theoretically the *exact* enantiomer of a chiral molecule (let us say of R configuration) from normal matter would be the S configuration of the same molecule from *antimatter* [41a] and again exact specular isomers would be the normal-S and anti-R from this compound. Experimental control of this picture presently is hindered by a "technical" obstacle, which is that the frontier research in production of antimatter atoms is now at anti-^{3}He [41b]. If it

becomes possible to prepare (small) chiral molecules from antimatter and to compare the characteristics of these with their "enantiomers" from normal matter, this certainly will be an important step towards obtaining a more accurate picture of racemates.

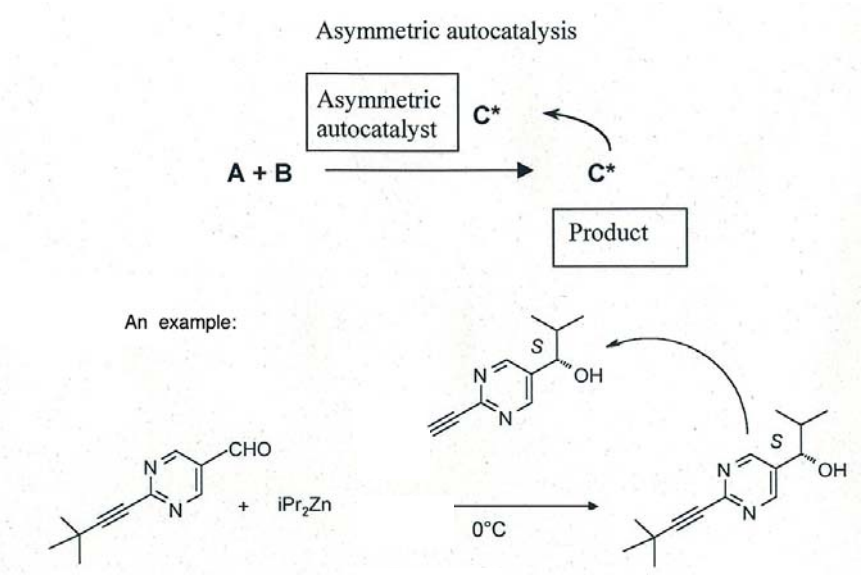
6. The Soai - Reaction

In course of studies regarding the origin the biological chirality, as well as during very practical research on the possibilities of enantioselective syntheses [16,17,23,38,39,42] the possibility of the "amplification" of chirality emerged [23,43]. This is essentially a chemical process, where a certain (molar) amount of enantiomeric excess is introduced and higher (molar) quantity of enantiomeric excess is obtained. The operation principle of such processes is similar to the signal-amplifying function of the classical triode. In an ideal case the "introduced" (less) and the "obtained" (more) enantiomeric excess is coming from the same compound – such systems are called *chiral autocatalytic reactions*. These reactions need not be catalytic in the stoichiometric sense. According to the best of our knowledge, until today, only one such reaction is known, the Soai-reaction [17,44-46]. Chemically this reaction is the (catalytic) alkylation of N-heterocyclic aldehydes with Zn-dialkyl (generally di-*iso*propyl) compounds, which yields heteroaryl-*iso*propyl-*sec*-alchools (Scheme 1).

The "chiral autocatalysis" is performed by this *sec*-alcohol, probably as being coordinated to the Zn atoms of the organometallic reagent [47a] obeying to fairly complicated kinetic conditions [47]. It is worth to mention that these kinetic conditions were established only *after* the particular nature of this alkylation reaction had been recognized by Kenso Soai and his team. A recent NMR study of the Soai-system provided significant elements for the identification of eventual intermediates [48].

Soai and coworkers performed experiments in an attempt to explore the limits of the efficiency of this reaction by adding the (product) alcohol with lower and lower enantiomeric excesses, which initiated the chiral autocatalytic process. In course of this work it has been found that even very low e.e., as 5×10^{-5} % of the product alcohol introduced initially in enantiopure form was sufficient to achieve more than 99.5% e.e. in the third run [49]. This fantastic result corresponds to a 630,000-fold multiplication of the initially "introduced" chirality.

In a next bold attempt, the Soai-group studied the



Scheme 1

behavior of the same system without any (enantiopure) chiral additive, that is, they made an attempt at the realization of the most rigorously formulated "absolute enantioselective synthesis". The results of these experiments were patented in 1997, and then published in 2003. [50]. The results (Fig. 2) apparently correspond to a statistical picture of racemates which has been discussed earlier in this paper: from 47 experiments in 18 cases significant enantiomeric excess of the R-alcohol, while in 19 cases that of the S-alcohol has been obtained. *This publication* [50] *is, in fact, a milestone in the history of the research on chemical chirality*, it can be regarded as the first, well-documented, experimental approach to a century-old theoretical problem. Soai's results provide an important experimental support to the hypothesis, that the racemates are to be described by the laws of statistics.

The "statistical" origin of Soai's absolute enantioselective synthesis can also be demonstrated using the very simple empirical formula found recently by our groups [51]:

$$\text{e.e.}_{product} = \text{e.e.}_{max} \frac{e.e._{start}}{B + e.e._{start}}$$

where $\text{e.e.}_{product}$ is the enantiomeric excess achieved by autocatalysis

e.e._{max} is the highest e.e. obtained by a certain experimental setup

e.e._{start} is the initial enantiomeric excess of the same compound which is the product (for the "first" cycles this was defined as the percentage of "added" enantiopure product with respect to the starting substrate)

B is a constant characteristic for the actual system.

Analyzing the (*t*-Bu-ethynyl)-pyrimidyl system of Soai [50] with this formula, one can "get back" the initial (statistical) enantiomeric excesses (e.e._{start}), which are inducing the results shown in Table 1 of ref. [50b]. We plotted these (calculated) initial e.e._{start} values against the "final" enantiomeric excesses ($\text{e.e.}_{product}$ in the second step) achieved experimentally (Fig. 3). This analysis shows some remarkable features:

(i) the calculated e.e._{start} range, extends from 2.5×10^{-12} to 1.5×10^{-10} % seems to be quite reasonable from the point of view of probability calculations (taking into

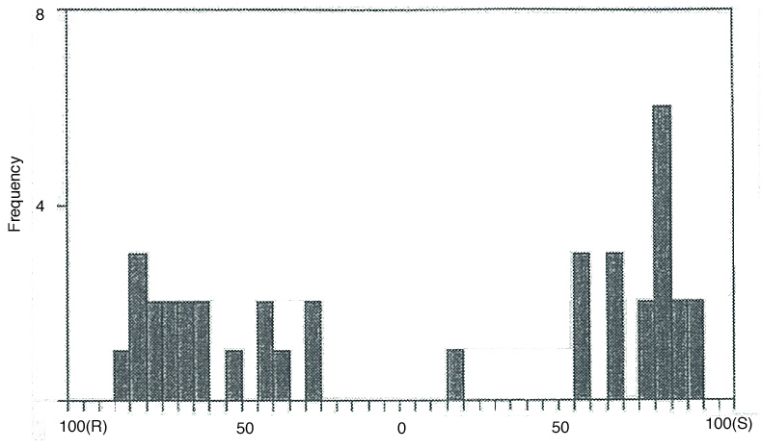


Figure 2.
Enantiomeric excess of the pyrimidyl-*sec*-alcohol in the Soai-reaction without chiral additive [50b]

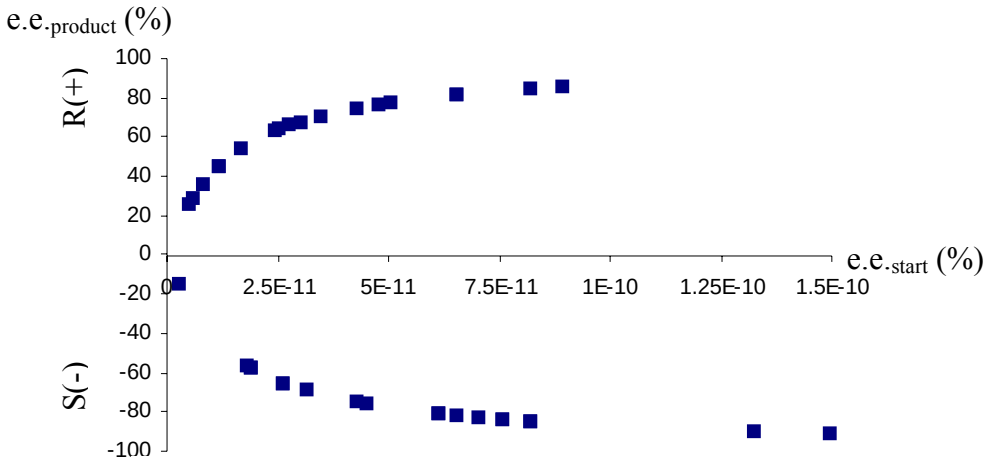


Figure 3.
"Statistical" e.e.$_{start}$ values correlated to the corresponding e.e.$_{product}$ results [50b, 51]

consideration the size of experiments used in ref. [50b] here Soai uses 0.1 mmol size experiment for the 1st cycle, this corresponds to Mills' e.e.$_{½} = 8.7 \times 10^{-9}$ %);

(ii) the symmetric shape of the two distributions (corresponding to R and S e.e.$_{max}$ values respectively) indicate equal (or very close) probabilities of the formation of the R and S isomers;

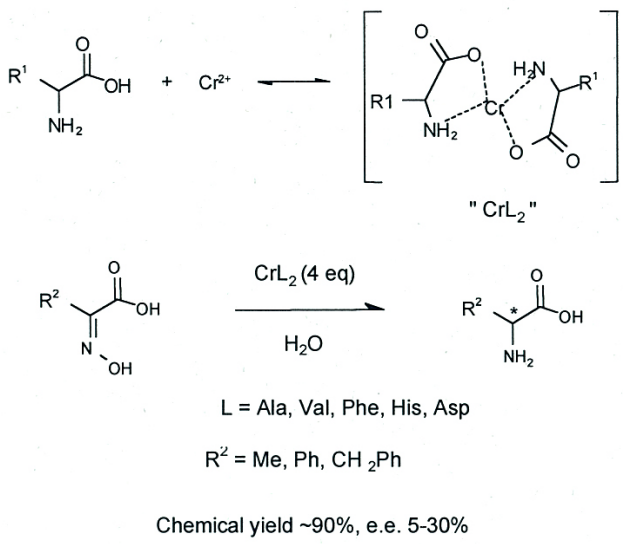
(iii) comparison of the range of e.e.$_{start}$ values with the most "optimistic" calculations of the NPV-generated (expected) "unavoidable" e.e. values [36] a small but systematic effect of the NPV influence on final e.e.$_{max}$ values could be predicted.

Several questions about the origin of biological chirality and about the nature of racemates remained, however, open. One of the most interesting open questions is, whether the statistical Soai-effect "hides" the effect of the weak nuclear forces? Perhaps, performing a major number of experiments[ii] a small but systematic preference in favor of one of the enantiomers could be detected? It is still an interesting question whether this favored enantiomer will be the same, which was predicted by theoretical MO calculations [36]? Most probably only a very large number of experiments will allow well founded conclusions.

For the moment, the question of the difference between the results of Soai's group [50] and of Singleton and Vo [26] is still open: while Soai and coworkers observed the preference of the two enantiomers in 1:1 (18:19) ratio, the latter Authors found a systematic and significant excess of one of the enantiomers. The difference might be due to a (dramatic) solvent effect (Soai: toluene/Et_2O, Singleton and Vo: toluene), but also to other (presently unknown) factors.

One of the most important open questions is, whether it will be possible to find other similar systems? This would be especially promising if these would be somewhat closer to biological systems than the aldehyde-alkylation with an organometallic reagent. The Authors of the present paper believe that the first small step in this direction has been made by the enantioselective reduction of (achiral) oximes of α-keto-carboxylic acids to the corresponding α-amino acids by complexes of chromium (II) with (natural) α-amino acids (Scheme 2) [53]. It should be pointed out that this reduction has two important

[ii] For the moment [50b] the average e.e. values obtained for 18 R-excess and 19 S-excess experiments show significant difference 62.88% and 72.67% respectively, but the spread of the σ values are much higher than the difference: ±18.92% and ±17.46% respectively.



Scheme 2

deficiencies with respect to the Soai-reaction: (a) the ligand amino acids and product amino acids are *not* the same and (b) it is much *less sensitive* than the Soai-reaction. Experimental efforts at improving these features are now in course in our Laboratories.

7. Epilogue

The modern (statistical) view of racemates is the result of a long scientific evolution. The speculative approach, however, became of immense practical significance only after the first experimental verifications [26,40,44,47,48,50], from these particularly the landmark papers of Soai [45f,50] may have an exceptional impact (*e.g.* [15b,17,54]) in the future.

The principles summarized in this review are not only of intellectual interest. The more profound understanding of the concept of racemates has a significant message for practical sectors as pharmaceutical research, organic fine chemistry ("deracemization"), applied materials science (e.g. liquid crystals) or environmental (more fashionably: green) chemistry.

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