How Long Have Nonlinear Effects Been Known in the Field of Catalysis?**

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Dedicated to Henri B. Kagan

A widespread belief in chemistry is that racemates and their constituent enantiomers do not differ in their scalar physical properties, such as boiling point. However, there is a series of examples which proves that this is not always the case. A particularly spectacular example is the boiling point of isopropyl trifluorolactate: Under normal pressure the (*S*)-enantiomer has a boiling point approximately 43 °C higher than that of the racemate.[1] This difference in boiling point allows the separation of a nonracemic mixture of this compound by fractional distillation! These differences in physical properties are due to the formation of diastereomeric aggregations which result from interactions between the two enantiomers. These interactions are also known to be the cause of unexpected sublimation phenomena[2] and NMR spectra.[3] At the beginning of the 1970s Horeau et al.[4] reported the first examples of the nonlinear relationship between optical purity and enantiomeric excess caused by diastereomeric aggregations. Further unusual results which were explained on the basis of enantiomeric interactions have been compiled by Noyori et al.[5]

The question as to what extent such a nonideal relationship effects chemical reactions goes back to Wynberg and Feringa.[6] Their well-known work led to the following proposition: "When a chiral substance undergoes a reaction, the reaction rate and the product ratio will depend—inter alia—upon the enantiomeric excess present in the starting material."[6a]

A logical continuation of this idea has recently led to nonlinear effects in asymmetric catalysis, first described quantitatively by Kagan and Agami et al. in 1986,[7] and these effects[8] are proving to be fruitful in asymmetric synthesis. A recent review on the subject contains not only the results obtained up to the present but also briefly discusses some possible future developments.[9]

The quantitative inclusion of the activity[10] in addition to the almost exclusively observed selectivity leads to a considerably better model and almost certainly to a better interpretation of the experimental results. The same treatment is also valid for product selectivity as a function of conversion.[11]

Until the appearance of the article by Kagan and Agami et al.,[7] it was generally accepted that the maximum *ee* value obtainable in an asymmetric synthesis was equal to the maximum *ee* value of the chiral auxiliary or chiral catalyst employed in the reaction [Eq. (1)].

$$ee_{\text{prod.}} = ee_0 ee_{\text{aux.}} \qquad (1)$$

Here ee_{prod} corresponds to the experimentally obtainable enantiomeric excess of the product, ee_0 is the value when the auxiliary or catalyst employed is optically pure, and ee_{aux} represents the enantiomeric excess of the auxiliary or catalyst. Practical experiments, however, have shown that there are deviations from the linear behavior: These deviations from linearity are designated as either positive or negative nonlinear effects.

Reactions with a positive nonlinear effect are particularly attractive. Starting from an optically impure catalyst in a reaction displaying a positive nonlinear effect, it is possible to obtain reaction products with a higher enantiomeric excess than is expected from the catalyst's optical purity. Essentially this represents an amplification of the chirality.

The model systems developed to explore this effect generally contain a variable number of rapidly exchanging chiral ligands (in the simplest case two, corresponding to the "ML_2 model") surrounding a reaction center. Under stationary conditions there are homo- and heterochiral complexes which lead to enantiomeric and racemic[12] products, respectively. Analogues of Equation (1) containing correction factors have been derived to give a quantitative description of these cases. The correction factors contain terms representing both the relative reactivities and the ratio between the hetero- and homochiral complexes, and it is these terms which cause

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the nonlinearity in the relationship between the experimentally obtained *ee* values of the product and the *ee* value of the starting material.

An impressive example of a positive nonlinear effect is the alkylation of benzaldehyde with diethylzinc in the presence of a catalytic amount of a chiral amino alcohol, such as 3-*exo*-dimethylaminoisoborneol.[5, 13] Even the addition of an amino alcohol with only a 15% enantiomeric excess (an optically very impure catalyst) leads catalytically to a product with a optical purity of about 95%—an incredible amplification of chirality!

The basic condition for the appearance of nonlinear effects in stereoselective reactions has been summarized by Kagan as follows: "The generation of diastereomeric species is the key feature that gives deviation from linearity".[9]

In connection with this a résumé published by Langenbeck[14] in 1936 appears astoundingly far-sighted: "It must be possible using a highly stereochemically specific catalyst, and where an equilibrium is formed with the substrate, to realize an increase in the optical purity when one allows an optically impure catalyst to catalyze a reaction starting with an optically impure substrate".[15]

The expression that Langenbeck first coined "Reinheitszunahme" (increase in optical purity) corresponds exactly in its content to what we understand nowadays in asymmetric synthesis as a "positive nonlinear effect".

The following quotations come from Langenbeck's work entitled "Theory of the Conservation and Origin of Optical Activity in Nature": "With every synthesis of an optically active compound from inactive starting materials, a degradation in optical purity takes place; that is, the newly formed compound is less optically active than the compound from which the optical activity was derived." The author continues: "If an enzyme is synthesized using another optically active enzyme, the newly formed product cannot be optically pure. The infinite repetition of these processes over a geological time period would have led to a complete loss of optical activity in enzymes (and therefore of all naturally occurring compounds) if the degradation in optical purity were not compensated for by an increase in optical purity in different processes."[15]

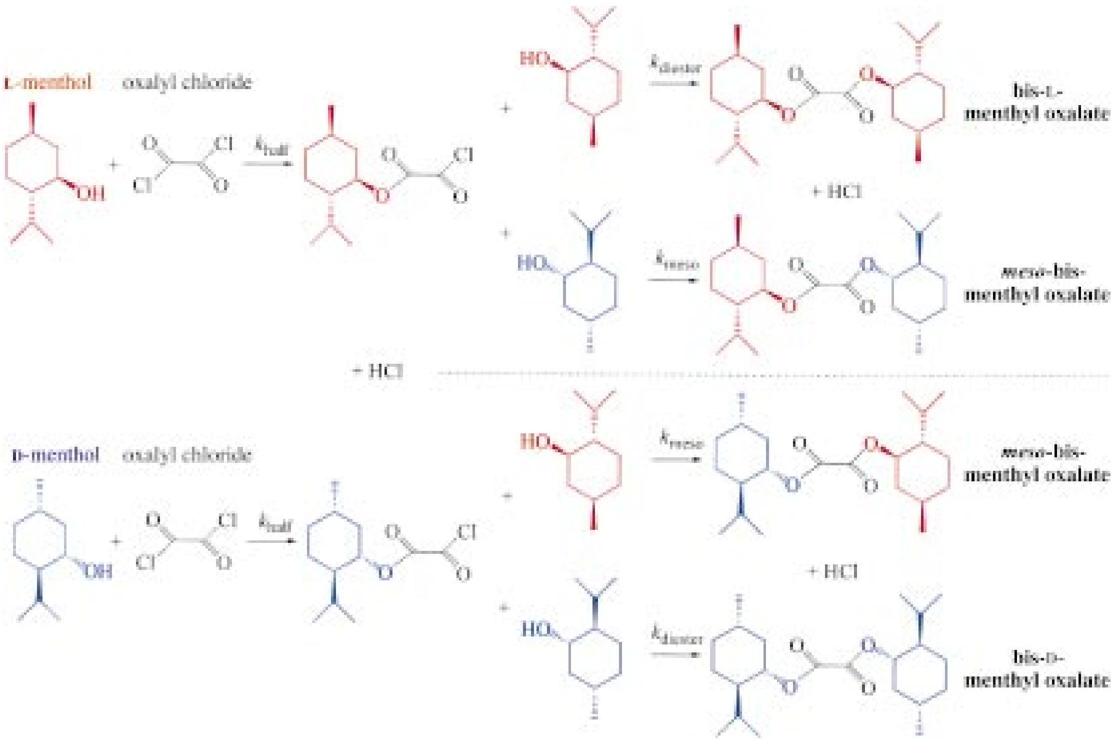
The reaction between L-menthol and oxalyl chloride was used as a simple model system for the experimental investigation of this postulated increase in optical purity (Scheme 1).

The results of the polarimetric determination of the angle of rotation of the product mixture, consisting of the optically active ester as well as the *meso* ester, are shown in Figure 1 (curve I). The optical purity of L-menthol used as the starting material was varied from racemic to optically pure.

Curve II in Figure 1 shows the optical rotation of the product diester, bis-L-menthyl oxalate, as a function of optical purity, thus providing a reference for curve I. Figure 2 shows the same experiment reevaluated using modern chromatographic techniques (HPLC) instead of the original polarimetric measurements.[16]

Although Langenbeck had no suitable analytical method for determining the proportion of *meso* ester present, he nevertheless correctly predicted the result: "If it were possible to separate the *meso* ester quantitatively, then it would be expected that even with use of L-menthol with a low *ee* value, an increase in the optical purity of the product would be observed".[15]

The results obtained with use of racemic menthol (0% *ee*) and optically pure L-menthol (100% *ee*) characterize the limiting values for a linear relationship in a graph of the *ee*



Scheme 1. Reaction sequence for the conversion of oxalyl chloride with optically enriched L-menthol.

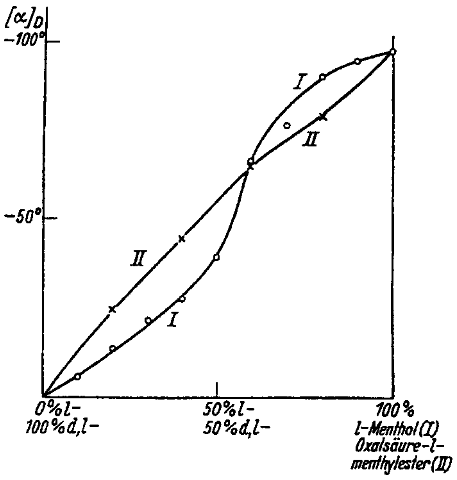


Figure 1. The increase in optical purity for the model reaction of L-menthol with oxalyl chloride reported by Langenbeck.[15] (The original figure is reproduced here with permission from Oldenbourg Wissenschaftsverlag GmbH. l-Menthol = L-menthol, Oxalsäure-l-menthylester = L-menthyl oxalate.)

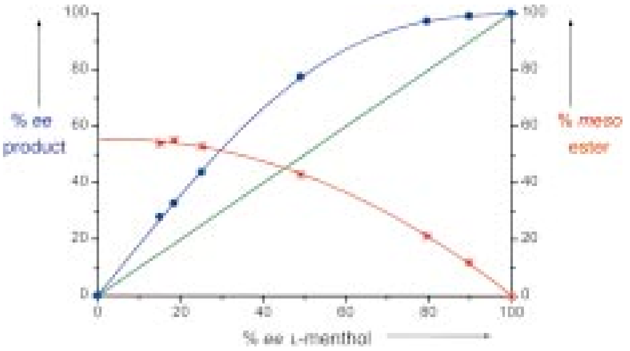


Figure 2. Plot of the enantiomeric excess (%) of the product as well as the percentage of *meso*-bis-menthyl oxalate as a function of the *ee* value (%) of the starting material. (A total of 5 g of the menthol mixture was treated with 50% of the stiochiometric amount of oxalyl chloride and worked up as described in ref. [15]. The resultant ester mixture was analyzed by HPLC.[16])

values of the product plotted against the *ee* values of the starting material. A positive deviation from this zero point line has been seen for all other *ee* values of menthol, corresponding to a positive nonlinear effect. The fundamental cause of this characteristic deviation is that the addition of optically impure as well as nonracemic menthol leads to the formation of the *meso* ester. The stoichiometry of the *meso* compound dictates that equal quantities of the two enantiomers of menthol are required for its formation. Hence, we always observe a larger *ee* value than expected for the optically active diester, in comparison to the *ee* value of the menthol used.[17] Consequently this reasoning forbids the existence of negative nonlinear effects. It is important to note that a linear relationship between the *ee* value of the starting material and the *ee* value of the product should always be observed in the case of complete turnover without formation of the *meso* compound.

The cause of the nonlinear effects discussed in Kagen's review[9] is the formation of an "intermediate" diastereomeric species. In contrast, the cause of the positive nonlinear effects described by Langenbeck is the formation of a diastereomeric product species.

There is not much literature about positive nonlinear chirality transfer or the practical applications of this effect for reactions which are neither catalytic reactions nor asymmetric syntheses.[18] Horeau et al. have described a variety of reaction variants.[19] By removal of the *meso* product and recovery of the starting material, the optical purity of the starting material can be increased. After several repetitions of this procedure it was possible to achieve optical purities of over 95% in many cases—starting from about 50%—in accordance with the quantitative equations on the basis of the statistical product distribution. Further examples of this "purification by duplication" are to be found in ref. [20]. The amplification effect observed by Langenbeck (Figure 2) itself does not represent a focal point of interest in all examples discussed so far, but has always been viewed as an intermediating effect.

The NMR spectroscopic determination of enantiomeric excess, for example in the case of alcohols, is an interesting application of the "*meso* effect". According to the principle which goes back to Feringa et al.[21] optically active compounds can be transformed with an achiral reagent such PCl_3. Under the condition of a statistical product distribution, it is then easily possible from the NMR spectrum to determine the relationship of the sum of each of the newly formed hetero- and homochiral compounds and therefore the enantiomeric excess of the optically active starting material. The amplification of the enantiomeric excess in the product is meaningless. Analogous approaches can be found in the literature.[22]

The mechanism for the formation of the bis-menthyl oxalate from the corresponding monoester is shown in Scheme 1. For simplicity the individual steps are assumed to be irreversible. The monoester is able to react to give the optically pure diester or the *meso* form. For these steps the rate constants (k_{diester} and k_{meso}) are, in principle, not equal. The resulting set of differential equations can be solved numerically.[23] When values are entered for the rate constants and starting concentrations of menthol and oxalyl chloride, the simulation provides the result presented in Figure 3; the reaction was followed to completion.

The simulations carried out can be summarized in the following way: A positive nonlinear effect is always observed for the product selectivity if nonracemic or optically impure

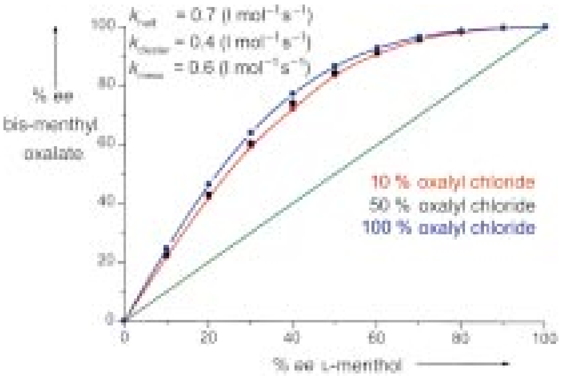


Figure 3. Calculated positive nonlinear effects for the reaction described in Scheme 1. Different starting values for oxalyl chloride were entered; 100% corresponds to the stoichiometric amount.

(scalemic) starting material is used, since the formation of the *meso* species is a necessary and sufficient condition for amplification of chirality. Even if the rate constants of the *meso* product formation are equal (i.e., a statistical distribution) or smaller than the rate constants of the diester formation, a positive nonlinear effect results. It is easy to understand that with more pronounced formation of the *meso* ester the positive nonlinear deviations also become larger, but at the cost of the yield of the optically enhanced product.

Reactions which are not pure dimerizations of the chiral starting material—in the diester formation shown in Scheme 1 the enantiomeric starting material is coupled through an oxalic acid unit—offer still another interesting aspect, namely, the variation of this component.

The simulation of various starting material concentrations of oxalyl chloride (from sub- to stoichiometric amounts) provide another degree of freedom, which leads to the following results: When $k_{\text{meso}} > k_{\text{diester}}$ (see Figure 3), the positive nonlinear effect with stoichiometric amounts of oxalyl chloride (100%) is larger than for substoichiometric amounts of oxalyl chloride. For the case where $k_{\text{meso}} < k_{\text{diester}}$ this is reversed, the largest positive nonlinear effects being observed when the quantity of oxalyl chloride used is far below the stoichiometric amount.

In connection with the variation of the amount of oxalyl chloride used, a possibly interesting parallel can be found to what has been described in the review[9] about nonlinear effects in asymmetric catalysis and stereoselective synthesis. What happens when the concentration of the chiral ligand is larger than is necessary for the formation of the homo- and heterochiral complexes? Under certain conditions a further amplification of chirality is to be expected.

The application of this "*meso* effect" is also conceivable for reactions which only work in the presence of a catalyst. An amplification of chirality is to be expected for a variant of the photocatalytic heterocyclization[24] of C_2-symmetric chiral alkynes with nitriles to give pyridines. It is possible that this type of amplification phenonenom, whether catalytic or stoichiometric, plays a role in the formation of the homochirality seen in nature.[25]

Wolfgang Langenbeck's visionary prediction made 60 years ago about an "increase in optical purity" in catalytic asymmetric synthesis is a current area of modern chemistry that is very closely connected with Kagan's work.

The formation of diastereomeric species is the prime and—in the usual case of nonequal reactivity of the hetero- and homochiral catalysts—a sufficient requirement for a nonlinear chirality transfer to be observed. If the diastereomorphic interactions take place in the catalyst, the result is a nonlinear effect in asymmetric synthesis and stereoselective reactions.

For the chiral amplification accompanying the formation of a diester from the reaction with a chiral alcohol, first described by Langenbeck, the diastereomeric interactions are transferred from the level of the intermediates to the level of the products. This means that these interactions do not play a role in the catalyst or auxiliary, but only in product formation. The consequences are differences in the reaction type as well as in the requirements of the starting material. The resulting reaction sequence is not an asymmetric synthesis or stereoselective reaction, but involves the use of a chirally enhanced starting material. A disadvantage is the unproductive formation of the *meso* compound, whereby the starting material can usually be recovered, however, only in racemic form. It would be possible to overcome this disadvantage by either manual methods or by a kinetic resolution followed by renewed use of the starting material. However, the long-known and also indirectly used approach represents an interesting variant of chirality amplification as only positive nonlinear effects can, in principle, occur and applications in catalytic reactions seem possible.

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[8] The term "nonlinear effect" is somewhat unfortunate, as other correlations such as the product selectivity as a function of the optical purity of a catalyst are also nonlinear. An example is the dependence of the logarithmic product ratio of selective reactions as a function of the reciprocal temperature (isoinversion principle): a) H. Buschmann, H.-D. Scharf, N. Hoffmann, P. Esser, *Angew. Chem.* **1991**, *103*, 480–515; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 477–515. b) D. Heller, H. Buschmann, *Top. Catal.* **1998**, *5*, 159–176. This nonlinear temperature dependence—the first work was carried out by Pracejus (H. Pracejus, *Justus Liebigs Ann. Chem.* **1960**, *634*, 9–22)—should be typical for all reactions displaying nonlinear effects in the "Kaganian" sense. The product enantiomers result from various reaction pathways.

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[12] For an uneven number of ligands, such as in the ML_3 model, the heterochiral species is not a *meso* compound, and this has a corresponding effect on product formation.

[13] M. Kitamura, S. Okada, S. Suga, R. Noyori, *J. Am. Chem. Soc.* **1989**, *111*, 4028–4036.

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[15] W. Langenbeck, G. Triem, *Z. Phys. Chem. A* **1936**, *177*, 401–408.

[16] The HPLC measurements were conducted using a Liquid Chromatograph 1090 from Hewlett Packard, equipped with a diode-array detector. The enantiomeric diester was separated from the *meso* form of the bis-menthyl oxalate on an achiral stationary phase Nucleosil NH_2 with 0.015% ethanol in hexane as the eluent. The separation of bis-D-menthyl oxalate from bis-L-menthyl oxalate and the *meso* form

was successful on a stationary phase Chiralcel OD-H (Daicel) with hexane as the eluent. Area factors between the optically pure diesters and the *meso* compound were disregarded, as these did not change the qualitative results.

[17] Amplification effects for a reaction of second or higher order that did not proceed with full conversion to products and which are not reducible to diastereomeric units were not investigated further due to the complexity of the problem. For example, if a nonracemic enantiomeric mixture reacted exclusively to give a homodimer product (2A → AA or 2B → BB) and if the conversion is less than 100%, the enantiomeric excess of the product is always larger than that of the starting material. Many examples of this type of amplification are discussed by a variety of authors in "Origins of Chiral Homogeneity in Nature": W. A. Bonner in *Topics in Stereochemistry*, *Vol. 18* (Eds.: E. L. Eliel, S. H. Wilen), Wiley, New York, **1988**, pp. 1–96.

[18] a) "Kinetic Resolution": H. B. Kagan, J. C. Fiaud in *Topics in Stereochemistry*, *Vol. 18* (Eds.: E. L. Eliel, S. H. Wilen), Wiley, New York, **1988**, pp. 249–330; b) V. Rautenstrauch, P. Megard, B. Bourdin, A. Furrer, *J. Am. Chem. Soc.* **1992**, *114*, 1418–1428.

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