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UNLIMITED NON-LINEAR SELECTIVITY EFFECTS IN SYSTEMS OF INDEPENDENT PARALLEL REACTIONS AS A BASIS FOR NEW CHEMICAL SEPARATION TECHNIQUES

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Abstract—There exist two basic types of kinetically controlled selective reactions. They differ fundamentally from each other with respect to the time dependence of the relative concentrations of the participating reactants. We call the first type, systems of dependent parallel reactions. They have in common the same ensemble of starting materials. The second type, systems of independent parallel reactions, have starting material ensembles that are distinguishable. The selectivity of dependent parallel reactions is limited by the ratio of their rate constants, whereas the selectivity of independent parallel reactions. An example is the recently developed synthesis of isomerically pure oligopeptides by similar manner. This follows from an analysis of the solutions of the corresponding differential equation systems. The non-linear and unlimited selectivity effects of independent parallel reactions may serve as a basis for new techniques to prepare pure chemical compounds from mixtures of chemical analogs that would be hard to separate by other means. Under suitable conditions this is possible, even if the reagents are also mixtures of chemical analogs. One of the most effective ways to synthesize isomerically pure chemical compounds is by beginning with a selective system of dependent parallel reactions, and then letting its products participate in a subsequent selective system of independent parallel reactions. An example, is the recently developed synthesis of isomerically pure oligopeptides by a stereoselective 4-component-condensation (4CC), followed by purification of the desirable diastereomer by preferential acidolysis of the other diastereomer (confer Scheme 6). Note that in such asymmetric syntheses the chiral reference system is exploited twice, first in the dependent parallel 4CC, and then in the independent parallel acidolysis. The overall stereoselectivity of such syntheses corresponds to the product of the selectivities of the consecutive steps.

INTRODUCTION

The topic of this paper is *chemical selectivity in kinetically controlled systems of parallel reactions.*

A reacting chemical system is kinetically controlled, if the relative amounts of the participating chemical compounds are determined before the system has attained thermodynamic equilibrium, otherwise it is thermodynamically controlled.[1,2] In the present context the fact is neglected that all chemical reactions reach, at least in principle, an equilibrium at some time.

A chemical reaction is ideally suited for synthetic purposes, if it produces the desired product ensemble in a quantitative yield, i.e. without conversion of the starting material ensemble, or any of its members, into other product ensembles.

Then the by-products are only those, which are due to the stoichiometry of the desired reaction. Generally, such by-products differ from the desired product so much with respect to some chemical, or physical property, that they are easy to remove by one of the customary separation techniques.

Only in very few exceptional cases do chemical reactions have this desirable property. For most syntheses one must be content with systems of *mutually dependent parallel* reactions, or more complex systems of parallel and consecutive *reactions*[4] that yield the desired product more or less preferentially, but yield also the products of competing side reactions. In this context one must take into account the possibility that the reactants may participate in more than one stoichiometric ratio.

The by-products from side reactions do not only correspond to losses in the overall yield of the main product, but they are also often hard to remove contaminants of the latter, and necessitate purification operations, which are limited to small scale preparations and are costly with regard to time and apparatus, and may cause product losses in the course of the separation operations.

The purification of the desired product by any of the customary methods is, as a rule, particularly difficult, if the contaminants are stereoisomers, or other close analogs of the main product. However, in many cases, there are no viable alternatives to syntheses through reactions, whose main products are accompanied by hard to remove by-products.

In this context, *systems of independent parallel reactions* are potentially useful, whose selectivity is not limited by rate constant ratios (Section 2). Suitably designed systems of independent parallel reactions, whose selectivity is a *steeply and non-linearly increasing function of certain rate constant ratios*, may serve as a basis for methods by which various types of chemical compounds can be isolated in a very pure state from mixtures of chemically analogous compounds, such as the

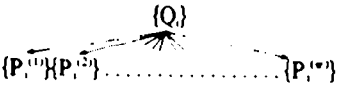
product mixtures which result from syntheses involving systems of mutually dependent parallel reactions.

Selectivity in systems of mutually dependent parallel reactions

A chemical reaction is the conversion of an ensemble $Q = \{Q_i | i = 1, \ldots, n_Q\}$ of starting material molecules Q_i into an isomeric ensemble $P = \{P_i | i = 1, \ldots, n_P\}$ of product molecules P_i.[3]

If two, or more distinct product ensembles $P^{(\pi)} = \{P_i^{(\pi)} | i = 1, \ldots, p^{(\pi)}\}$ $(j = 1, \ldots, \pi)$ are formed from Q in a reacting chemical system under given non-equilibrium conditions we have a *kinetically controlled pair*, or *family* of *mutually dependent parallel reactions* (Scheme 1).

In this case none of the product molecules $P_i^{(\pi)}$ must be identical with one of the starting material molecules.



Scheme 1.

The term "mutually dependent reactions" refers to the fact that all of the considered reactions have in common the same ensemble of starting material molecules $\{Q_i\}$, and each molecule Q_i of the latter participates in each reaction. The system of mutually dependent parallel reactions has the property of selectivity, if at least one of the product ensembles differs from the other product ensembles with respect to its relative amount.

For any pair of product ensembles $\{P_i^{(\mu)}\}, \{P_i^{(\nu)}\}$ the ratio of their concentrations, p_μ, p_ν is $p_\mu/p_\nu = k_\mu/k_\nu = e^{(G_\nu^\ddagger - G_\mu^\ddagger)/kT}$ at any instant of the reaction, with k_μ, k_ν as the rate constants of the respective reactions, and $G_\mu^\ddagger$, $G_\nu^\ddagger$ the free enthalpies of their transition states.

Thus the concentration ratios p_μ/p_ν of any products $P_i^{(\mu)}$ remain constant throughout the whole reaction, and so do the concentration ratios q_i/q_j of the starting materials, if initially they are present in the relative stoichiometric amounts that are needed for the reactions.

If the products $\{P_i^{(\mu)}\}$ differ by their chemical constitution we have a reacting system with *constitutional selectivity*. If they are stereoisomers, this system of interdependent parallel reactions is *stereoselective*, and is a *family of corresponding reactions* whose stereoselectivity is interpreted in a generalized way by the stereochemical analogy model.[2,4]

According to the Curtin–Hammet principle,[5] the same considerations apply also to systems of parallel reactions which do not originate from a single ensemble of starting materials $\{Q_i\}$, but from an equilibrium system of isomeric ensembles of starting materials which interconvert rapidly relative to the rates of the product-forming reactions.[2]

Selectivity in systems of independent parallel reactions

Let $Q = \{Q_1, \ldots, Q_{n_Q}\}$ be an ensemble of molecules representing the molecular species Q_i which are contained in a mixture of chemical compounds, and let $Q^{(\mu)}$ be distinct subsets of $Q = \bigcup_\mu Q^{(\mu)}$ which react under the given conditions to form product ensembles $P^{(\mu)}$ with rate constants $k^{(\mu)}$.

Such a system of parallel reactions is called *independent* because none of individual reactions have in common the same subset $Q^{(\mu)}$ of Q as the starting material ensemble.

A system of independent parallel reactions is selective, if the rates of the individual reactions are different, and

$$Q^{(1)} \xrightarrow{k^{(1)}} P^{(1)}$$
$$Q^{(2)} \xrightarrow{k^{(2)}} P^{(2)}$$
$$\vdots$$
$$Q^{(\pi)} \xrightarrow{k^{(\pi)}} P^{(\pi)}$$

Scheme 2.

the rate differences are not only due to differences in the initial concentrations of the starting materials.

Selective systems of independent parallel reactions do not only yield the products $P^{(\mu)}$ in different relative amounts, but they do also change the relative amounts of the starting materials belonging to the set Q.

This particular feature of independent parallel reactions leads to their potential usefulness for the preparation of very pure chemical compounds from product mixtures. It will be shown in the following sections that independent parallel reactions can be used to convert the chemically closely similar analogs of the desired main products of syntheses into compounds which differ from the main product so much with regard to their chemical and physical properties, that they can be removed effectively by the customary methods, and that this purification can be carried out with relatively small losses of the main product, with a selectivity which can be much higher than the relevant ratios of rate constants.

The history of studies in the field of what we now call systems of independent parallel reactions is closely connected with the interest in the conversion of racemates into optically active compounds, and the question of the origin of optically active organic compounds.

As early as in 1908, Bredig and Fajans[7] (see also Refs. 8 and 9) derived equations of the type (1) (Ref. 9).

$$\frac{c_R - c_S}{c_R + c_S} = \tanh 1/2(k_S - k_R)t \qquad (1)$$

to represent the formation of optically active compounds from racemates by preferential enzymatic destruction of one of the enantiomers. The somewhat related time dependence of the enantiomeric purity during a kinetic resolution has been discussed by Mislow *et al.*[10] in the context of the asymmetric reduction of a racemic ketone.

The reaction of chiral acylating agents with racemic primary amines was studied by Herlinger *et al.*[11] with respect to the relation between the relative amounts of the reactants and the products.

Probably the best known examples for pairs of independent parallel reactions are the conversions of racemates into optically active compounds by stereoselective photolysis with circularly polarized light.

In 1930 Kuhn and Knopf[12] investigated the photolysis of N,N-dimethyl α-azidopropionamide by circularly polarized light. After 40% had been photolysed, the residual starting material was optically active with an enantiomer excess (EE) of 0.5%.

Kagan *et al.*[9] succeeded in producing camphor with 20% enantiomer purity by photodecomposing racemic camphor to the extent of 99%, in accordance with eqn (1), and in analogy to the experiments of Kuhn and Knopf.[12]

Recently Decker[13] has published a series of papers on the kinetic resolution of racemates by complex kinetic

systems involving autocatalysis and its selective inhibition by certain reaction products.

To our knowledge, hitherto the non-linear selectivity effects of independent parallel reactions have not been used as a means of preparing pure compounds from product mixtures that are formed by synthetic reactions, and no general and systematic discussion of independent parallel reactions with selectivities beyond rate constant ratios has yet been published.

Representative cases of independent parallel reactions with non-linearly increasing selectivity

Independent first order and pseudo-first order pairs of parallel reactions. In a reacting chemical system containing two chemical compounds Q and $\bar{Q}$ which both undergo first, or pseudo-first order reactions according to Scheme 3, there is an exponential increase of selectivity with respect to the relative amounts of the unreacted starting materials Q and $\bar{Q}$.

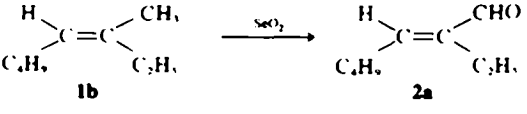
$$Q \xrightarrow{k} P$$

$$\bar{Q} \xrightarrow{\bar{k}} \bar{P}$$

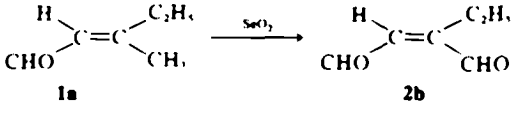
Scheme 3.

For example, such systems of independent parallel reactions are the selective oxidation of **1** by large excess of SeO_2,[14] or the stereoselective hydrolysis or **3a** and **3b** by a large excess of hydroxide ion, or the stereoselective acidolysis **10**→**11** of diastereosomeric peptide derivatives,[15] whose mixtures are produced by stereoselective 4-component-condensations,[16–21] (Fc: Ferrocenyl, **6** and **9**: α-amino acid, or peptide derivatives).

Note that Scheme 6 represents a stereoselective pair of dependent parallel 4CC whose products **10a** and **10b** are



1b **2a**



1a **2b**

Scheme 4.[14]

the starting materials of a pair of independent parallel acidolyses. Here, the overall ratio of the amounts of products **10a** and **10b**, as well as the ratio of **11a** and **11b**, which is obtained by total acidolysis of the latter mixture of **10a** and **10b**, corresponds to the product of selectivities of the two consecutive systems of parallel reactions. This reflects the fact that Scheme 6 describes an asymmetric synthesis in which the chiral template, the α-ferrocenyl alkyl system is exploited twice, first in the 4CC step, and then again in the acidolysis.

Thus the overall selectivity is determined by the product of the selectivities of the individual successive steps. An early example of selectivity multiplication[19] in such systems of reactions was found by Kleimann and Ugi in 1967.[16]

The concentrations q(t) and $\bar{q}(t)$ of Q and $\bar{Q}$ (Scheme 3) at the time t are described by eqns (2a) and (2b), or (3a) and (3b), respectively. In the latter equations we have $t_{1/2}$, the half-life time of Q, as the time unit, i.e. $\tau = t/t_{1/2}$ and $x = \bar{k}/k$.

$$q(t) = q(0) \cdot e^{-kt} \tag{2a}$$

$$\bar{q}(t) = \bar{q}(0) \cdot e^{-\bar{k}t} \tag{2b}$$

$$q(\tau) = q(0) \cdot 2^{-\tau} \tag{3a}$$

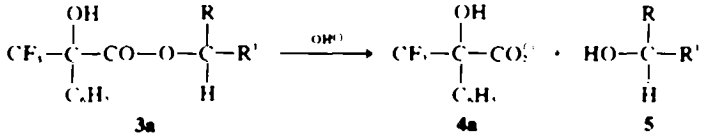
$$\bar{q}(\tau) = \bar{q}(0) \cdot 2^{-x\tau} \tag{3b}$$

According to eqn (4) which is obtained from (3a) and (3b), the selectivity of this system with respect to Q and $\bar{Q}$ increases exponentially with $(x-1)\tau$

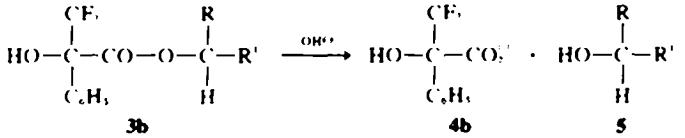
$$\frac{q(\tau)}{\bar{q}(\tau)} = \frac{q(0)}{\bar{q}(0)} 2^{(x-1)\tau}. \tag{4}$$

Let us assume that a synthetic reaction produces a mixture of the main product Q and a by-product $\bar{Q}$. If this mixture reacts according to Scheme 3, and we have $x > 1$, then the ratio of the relative amounts of Q and $\bar{Q}$ changes in favor of Q. If one terminates the reactions at a time such that $(x-1)\tau = 10$ the ratio $q(\tau)/\bar{q}(\tau)$ changes from $q(0)/\bar{q}(0)$ by a factor of $2^{10} \approx 1000$ in favor of Q. Thus, for example, a 50:50 mixture of Q and $\bar{Q}$ is converted into a 99.9:0.1 mixture, by letting the reactions proceed till $(x-1)\tau = 10$, and then separating the unreacted compounds $Q + \bar{Q}$ from the products $P + \bar{P}$.

Since the change in the relative amounts of Q and $\bar{Q}$ increases with $2^{(x-1)\tau}$, the yield of Q with a specified degree of purity from a given mixture of Q and $\bar{Q}$ increases steeply with x. This is due to the fact that, the higher x, the shorter will be the time τ which is needed to reach a certain value of $2^{(x-1)\tau}$, and the higher therefore will be the yield $2^{-\tau}$ of purified Q (eqn 2a).

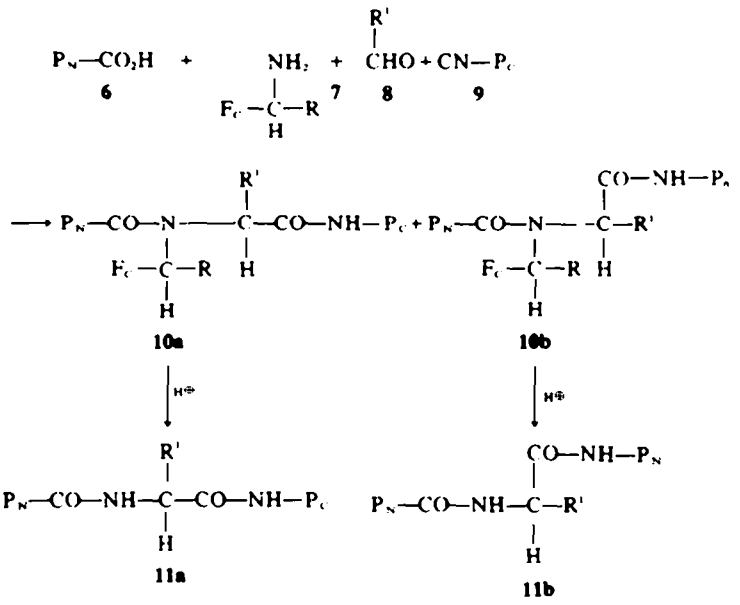


3a **4a** **5**



3b **4b** **5**

Scheme 5.[17]



This is illustrated by Fig. 1. The straight line with unit slope represents the change of the $\log_2$ of the ratio $q(\tau)/\bar{q}(\tau)$, or the relative purity of Q, respectively, on the left hand vertical coordinate axis as a function of $(x-1)\tau$, on the lower horizontal axis. Figure 1 also represents $\log_2(q(\tau)/q(0))$, or the percentage yield of "purified" Q; on the right hand vertical coordinate axis as a function of τ (on the upper horizontal coordinate axis).

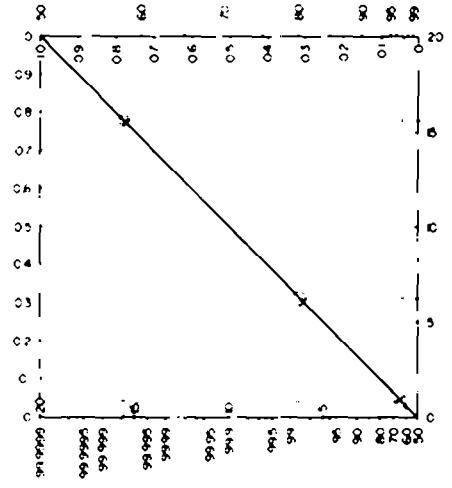


Fig. 1. The time-dependence of the enrichment in Q of a mixture of two chemical compounds Q and $\bar{Q}$ which react by first-order, or pseudo first-order reactions with different rate constants k and $k = xk$ $(x > 1)$, and the yield of Q as a function of the elapsed time τ.

This diagram may be used to determine how long a mixture of Q and $\bar{Q}$ with a given initial ratio $q(0)/\bar{q}(0)$ must react in order to obtain a certain value for $q(\tau)/\bar{q}(\tau)$, and what the yield of Q will then be.

For example one finds that a 98.5/1.5 mixture of Q and $\bar{Q}$ (point ⊙ in Fig. 1) corresponds to $(x-1)\tau = 6.2$ and a 99.998/0.002 mixture to $(x-1)\tau = 15.6$ (point □ in Fig. 1). With an assumed value of 230 for $(x-1)$ we have $\tau = (5.6 - 6.2)/230 = 0.0409$. From this follows $\log_2(q(t)/q(0) = 0.0409)$ which corresponds to a 97.2% yield of Q. Figure 1 may equally well be used to determine $t_{1/2}$ and x from model experiment data. If a 97.2% yield of Q is obtained after 61.35 min, we have $t_{1/2} = 63.35/0.0409 = 1500$ min for Q, and if the purity of Q changes at the same time from 98.5 to 99.998% we have $x = 231$. This example refers to a recent purification of a peptide derivative which had been obtained by a stereoselective 4CC[20] according to Scheme 6.

Combination of (3a) and (3b) and elimination of τ yields:

$$\left(\frac{q(\tau)}{q(0)}\right)^x = \left(\frac{\bar{q}(\tau)}{\bar{q}(0)}\right). \qquad (5)^{22}$$

If the time dependence is of no interest, eqn (5) may also be used to correlate the purity and yield of Q.

Table 1 illustrates the relationship of the yield and purity of Q with x.

According to eqn (4) and (5) one can obtain Q in unlimited purity from any mixture of Q and $\bar{Q}$, if $x > 1$. One must only be willing to sacrifice the corresponding relative amount of Q.

In reality there are, obviously, various limitations to the attainable purity of Q. On one hand, the fact that all chemical reactions are, at least in principle, equilibria limits $q(\tau)/\bar{q}(\tau)$. On the other hand, the separability of $P + \bar{P}$ from $Q + \bar{Q}$ can also be a limiting factor. Further the mixtures of Q and $\bar{Q}$ do, in real chemistry, always contain some further compounds which are hard to remove.

The selectivity of the reactions according to Scheme 3 with respect to P and $\bar{P}$ is described by eqn (6).

$$\frac{p(\tau)}{\bar{p}(\tau)} = \frac{q(0) - q(\tau)}{\bar{q}(0) - \bar{q}(\tau)} = \frac{q(0)}{\bar{q}(0)} \cdot \frac{1 - 2^{-\tau}}{1 - 2^{-x\tau}}. \qquad (6)$$

With $\tau \to 0$ we have (7),

$$\frac{p(\tau)}{\bar{p}(\tau)} \to \frac{q(0)}{\bar{q}(0)} \cdot \frac{1}{x}. \qquad (7)$$

Table 1. Per cent yield of purified Q [100% · q(τ)/q(0)], computed with given values of per cent initial purity: π(0) = 100% · q(0)/[q(0) + q̄(0)], and final purity: π(τ) = 100% · q(τ)/[q(τ) + q̄(τ)] and with given values of rate constants x = k̄/k

π(τ) %	π(0) %	x = 2.5	5	10	20	40	80	160	320
99.9	10	0.3	10.3	36.4	62	79.2	89.2	94.5	97.2
99.9	30	0.6	14.4	42.3	66.5	82	90.7	95.3	97.6
99.9	50	1.1	17.8	46.5	69.6	83.8	91.7	95.8	97.9
99.9	70	1.8	22	51.1	72.7	85.7	92.7	96.3	98.2
99.9	80	2.6	25.2	54.2	74.8	86.9	93.3	96.6	98.3
99.9	90	4.4	30.9	59.3	78.1	88.7	94.3	97.1	98.6
99.9	95	7.2	37.2	64.4	81.2	90.4	95.2	97.6	98.8
99.9	98	13.4	47.1	71.6	85.4	92.6	96.3	98.2	99.1
99.9	99	21.5	56.2	77.4	88.6	94.3	97.2	98.6	99.3
99.99	10	0.1	5.8	28.2	54.9	74.7	86.6	93.1	96.5
99.99	30	0.2	8.1	32.8	58.9	77.3	88.1	93.9	96.9
99.99	50	0.3	10.1	36	61.6	79	89	94.4	97.2
99.99	70	0.4	12.4	39.5	64.4	80.7	90	94.9	97.5
99.99	80	0.6	14.2	42	66.3	81.9	90.6	95.2	97.6
99.99	90	1	17.4	45.9	69.2	83.6	91.6	95.7	97.9
99.99	95	1.6	20.9	49.9	72	85.2	92.4	96.2	98.1
99.99	98	2.9	26.5	55.4	75.6	87.3	93.5	96.8	98.4
99.99	99	4.7	31.6	59.9	78.5	88.9	94.4	97.2	98.6
99.999	10	0.1	3.3	21.8	48.6	70.4	84.1	91.8	95.8
99.999	30	0.1	4.6	25.4	52.2	72.9	85.6	92.6	96.2
99.999	50	0.1	5.7	27.9	54.6	74.5	86.5	93.1	96.5
99.999	70	0.1	7	30.6	57.1	76.1	87.4	93.6	96.8
99.999	80	0.2	8	32.5	58.7	77.2	88	93.9	96.9
99.999	90	0.3	9.8	35.6	61.3	78.8	88.9	94.4	97.2
99.999	95	0.4	11.8	38.6	63.8	80.3	89.8	94.8	97.4
99.999	98	0.7	14.9	42.9	67	82.3	90.9	95.4	97.7
99.999	99	1	17.8	46.4	69.5	83.8	91.7	95.8	97.9

With increasing xτ, e.g. xτ > 10, p(τ)/p̄(τ) approaches (1 − 2 ′)q(0) and with decreasing τ it goes towards the upper bound q(0)/xq̄(0) (eqn (7) in Table 2). Accordingly the selectivity of this system with respect to P and P̄ cannot be used as effectively for the preparation of pure compounds, as it is possible by the selectivity with respect to Q and Q̄.

Pairs of independent higher order parallel reactions. Let Q and Q̄ be two distinct chemical compounds which react with a partner R according to Scheme 7 (k̄ = xk), x > 1)

The reactions according to Schemes 4 and 5 are examples of such systems of independent second order parallel reactions, if the reaction partners of 1, or 3, respectively (alkaline hydroxide in Scheme 4, and SeO_2 in Scheme 5) are not used in a large excess.[11]

The rates of these reactions are given by eqn (8a) and (8b)

$$\frac{dq(t)}{dt} = k \cdot q(t) \cdot r(t) \tag{8a}$$

$$\frac{d\bar{q}(t)}{dt} = \bar{k} \cdot \bar{q}(t) \cdot r(t). \tag{8b}$$

Since none of these expressions vanishes with finite

$$Q + R \xrightarrow{k} P$$

$$\bar{Q} + R \xrightarrow{\bar{k}} \bar{P}$$

Scheme 7.

q(0), q̄(0), r(0) and t, we may divide (8a) by (8b) to yield (9), and then (10)–(12).

$$\frac{dq(t)}{d\bar{q}(t)} = \frac{k \cdot q(t)}{\bar{k} \cdot \bar{q}(t)} \tag{9}$$

$$x \int_{q(0)}^{q(t)} \frac{dq(t)}{q(t)} = \int_{\bar{q}(0)}^{\bar{q}(t)} \frac{d\bar{q}(t)}{\bar{q}(t)} \tag{10}$$

$$x \ln [q(t)/q(0)] = \ln [\bar{q}(t)/\bar{q}(0)] \tag{11}$$

$$\left(\frac{q(t)}{q(0)}\right)^x = \left(\frac{\bar{q}(t)}{\bar{q}(0)}\right). \tag{12}$$[22]

Note that eqn (12) corresponds to (5), and that Table 1 is also pertinent for reactions according to Scheme 7.

If R had not only represented a single reactant, but an ensemble of two, or more reactants, and r(t) had been the product of their concentrations, we would still have obtained eqn (12) because r(t) cancels out. Thus eqn (12) represents quite generally the selectivity of a wide range of kinetic systems.

It is to be noted that the observable ratio q(t)/q̄(t) of parallel reactions according to Scheme 7 is independent of the relative initial concentration of R, and depends only upon x = k̄/k and the initial concentration of Q and Q̄, as long as the initial concentration r(0) of R suffices stoichiometrically for the required consumption of Q and Q̄.

If Q and Q̄ are enantiomers, i.e. q(0) = q̄(0), and R is a chiral reagent, the ratio q(t)/q̄(t) increases monotonously with time, till either Q, or R has been totally consumed. With a sufficiently high value of r(0) and an appropriate

timing for the termination of the reaction, such reactions can be used for the preparation of remarkably pure enantiomers Q from racemic mixtures of Q and $\bar{Q}$.

For example, with $x = 20$, $q(0) = \bar{q}(0) = 1$ and $q(t) = 0.8$ we have

$$\bar{q}(t) = (0.8)^{20} = 0.01153.$$

Any initial concentration $r(0) \geq 0.01153$ of R can be used to change the concentration ratio of $q(0)/\bar{q}(0) = 1$ to $q(t)/\bar{q}(t) = 69.38$, i.e. the initial 1:1 mixture of Q and $\bar{Q}$ into a mixture of 98.58% Q and 1.42% $\bar{Q}$. If the initial concentration is precisely sufficient to reach this ratio of $q(t)/\bar{q}(t)$, then theoretically the reaction will take infinite time. The higher r(0), the sooner this ratio is attained.

Quadruplets of second order parallel reactions, and the preparation of optically pure chiral compounds from a racemate and a partially resolved racemate. Let Q and $\bar{Q}$ be enantiomers which are capable of reacting with another pair of enantiomers R and $\bar{R}$ according to Scheme 8.

$$Q + R \xrightarrow{k} (QR)$$
$$Q + \bar{R} \xrightarrow{k} (Q\bar{R})$$
$$\bar{Q} + R \xrightarrow{k} (\bar{Q}R)$$
$$\bar{Q} + \bar{R} \xrightarrow{k} (\bar{Q}\bar{R}).$$

Scheme 8.

These reactions are represented by the differential eqns (12a)–(12d).

$$-\frac{dq(t)}{dt} = q(t)[kr(t) + \bar{k}\bar{r}(t)] \tag{12a}$$

$$-\frac{d\bar{q}(t)}{dt} = \bar{q}(t)[\bar{k}r(t) + k\bar{r}(t)] \tag{12b}$$

$$-\frac{dr(t)}{dt} = r(t)[kq(t) + \bar{k}\bar{q}(t)] \tag{12c}$$

$$-\frac{d\bar{r}(t)}{dt} = \bar{r}(t)[\bar{k}q(t) + k\bar{q}(t)]. \tag{12d}$$

This system of differential equations cannot be solved explicitly, but only numerically.

With $\bar{k}/k = x > 1$ the reaction of a mixture of Q and $\bar{Q}$ with $q(0) \geq \bar{q}(0)$ and a mixture of R and $\bar{R}$ with $r(0) > \bar{r}(0)$ leads always to an enrichment of Q vs. $\bar{Q}$. With such systems of independent parallel reactions it is, in fact, possible to obtain Q in any desired degree of optical purity from a racemate $Q + \bar{Q}$, or a mixture of Q and $\bar{Q}$ which contains Q in excess over $\bar{Q}$ by reacting $Q + \bar{Q}$ with a mixture of $R + \bar{R}$ containing more R than $\bar{R}$. Tables 3 and 4 and Figs. 2 and 3 illustrate the reaction of a racemate $Q + \bar{Q}$ with a partially resolved racemate $R + \bar{R}$ of 90% EE, or 10% EE respectively. These examples demon-

Table 2. The product selectivity increase factor $w(x, \sigma) = (1 - 2^{-\sigma})/(1 - 2^{-\tau})$ as a function of the yield of the product $\bar{Q}$: $\rho(\tau) = 1 - 2^{-\tau}$

τ	$\rho(\tau)$	x = 2.5	5	10	20	40	80	160	320
0.0001	0.01	2.499	4.998	9.994	19.98	39.92	79.68	158.7	314.9
0.0014	0.1	2.498	4.99	9.955	19.81	39.23	76.92	147.9	274
0.0145	1	2.481	4.901	9.562	18.21	33.1	55.25	79.97	95.99
0.0291	2	2.463	4.804	9.146	16.62	27.71	40.07	48.03	49.92
0.074	5	2.407	4.524	8.025	12.83	17.43	19.67	19.99	20
0.152	10	2.316	4.095	6.513	8.784	9.852	9.998	10	10
0.3219	20	2.138	3.362	4.463	4.942	4.999	5	5	5
1	50	1.646	1.938	1.998	2	2	2	2	2
2.3219	80	1.228	1.25	1.25	1.25	1.25	1.25	1.25	1.25
3.3219	90	1.108	1.111	1.111	1.111	1.111	1.111	1.111	1.111
4.3219	95	1.052	1.053	1.053	1.053	1.053	1.053	1.053	1.053
5.6439	98	1.02	1.02	1.02	1.02	1.02	1.02	1.02	1.02
6.6439	99	1.01	1.01	1.01	1.01	1.01	1.01	1.01	1.01
9.9658	99.9	1.001	1.001	1.001	1.001	1.001	1.001	1.001	1.001
13.2877	99.99	1	1	1	1	1	1	1	1

Table 3. (a)...(e) The reaction of racemic $Q + \bar{Q}$ ($q = \bar{q} = 1.0$) with an equivalent amount of partially resolved racemate $R + \bar{R}$ ($r = 1.9$, $\bar{r} = 0.1$, i.e. 90% EE) and different values of $x = \bar{k}/k$: (a) $x = 3$, (b) $x = 10$, (c) $x = 30$, (d) $x = 100$, (e) $x = 300$. Tables 3(a)...(e) and Fig. 2(a)...(e) are mutually complementary

Table 3(a)

	K: 1.0				$\bar{K}$: 3.0	
T	Q	$\bar{Q}$	R	$\bar{R}$	$Q/(Q+\bar{Q})$ (×100)	$R/(R+\bar{R})$ (×100)
0.0000	1.00000	1.00000	1.90000	0.10000	50.000	95.000
1.0000	0.39450	0.08165	0.46292	0.01322	82.852	97.224
2.0000	0.26823	0.02737	0.29080	0.00480	90.742	98.378
3.0000	0.20678	0.01288	0.21733	0.00233	94.137	98.940
4.0000	0.16932	0.00717	0.17517	0.00132	95.937	99.254
5.0000	0.14377	0.00443	0.14738	0.00082	97.013	99.446
6.0000	0.12512	0.00293	0.12751	0.00055	97.709	99.573
7.0000	0.11085	0.00205	0.11252	0.00038	98.186	99.661
8.0000	0.09956	0.00149	0.10077	0.00028	98.528	99.724
9.0000	0.09040	0.00112	0.09130	0.00021	98.781	99.771
10.0000	0.08279	0.00086	0.08349	0.00016	98.974	99.807

Table 3(b)

	K: 1.0				K̄: 10.0	
T	Q	Q̄	R	R̄	Q/(Q + Q̄) (× 100)	R/(R + R̄) (× 100)
0.0000	1.00000	1.00000	1.90000	0.10000	50.000	95.000
0.1500	0.76944	0.15930	0.90295	0.02579	82.848	97.223
0.3000	0.66775	0.04861	0.70765	0.00872	93.214	98.783
0.4500	0.60004	0.01813	0.61480	0.00336	97.068	99.456
0.6000	0.54797	0.00756	0.55411	0.00142	98.639	99.744
0.7500	0.50533	0.00341	0.50810	0.00064	99.329	99.873
0.9000	0.46929	0.00164	0.47062	0.00031	99.652	99.934
1.0500	0.43822	0.00083	0.43889	0.00016	99.811	99.964
1.2000	0.41110	0.00044	0.41145	0.00008	99.893	99.980
1.3500	0.38717	0.00024	0.38736	0.00005	99.938	99.988
1.5000	0.36589	0.00014	0.36600	0.00003	99.963	99.993

Table 3(c)

	K: 1.0				K̄: 30.0	
T	Q	Q̄	R	R̄	Q/(Q + Q̄) (× 100)	R/(R + R̄) (× 100)
0.0000	1.00000	1.00000	1.90000	0.10000	50.000	95.000
0.0100	0.95832	0.60538	1.48971	0.07399	61.286	95.268
0.0200	0.92723	0.40094	1.27267	0.05550	69.813	95.821
0.0300	0.90294	0.27945	1.14035	0.04204	76.365	96.444
0.0400	0.88331	0.20122	1.05243	0.03209	81.447	97.041
0.0500	0.86698	0.14814	0.99049	0.02464	85.407	97.573
0.0600	0.85307	0.11083	0.94489	0.01901	88.502	98.028
0.0700	0.84096	0.08391	0.91014	0.01473	90.927	98.407
0.0800	0.83021	0.06413	0.88288	0.01146	92.830	98.719
0.0900	0.82050	0.04937	0.86093	0.00894	94.325	98.972
0.1000	0.81161	0.03823	0.84285	0.00700	95.501	99.177

Table 3(d)

	K: 1.0				K̄: 100.0	
T	Q	Q̄	R	R̄	Q/(Q + Q̄) (× 100)	R/(R + R̄) (× 100)
0.0000	1.00000	1.00000	1.90000	0.10000	50.000	95.000
0.0100	0.92514	0.24645	1.13337	0.03822	78.965	96.738
0.0200	0.89299	0.08764	0.96523	0.01541	91.063	98.429
0.0300	0.87573	0.03457	0.90394	0.00636	96.202	99.301
0.0400	0.86431	0.01422	0.87586	0.00267	98.381	99.697
0.0500	0.85531	0.00597	0.86016	0.00113	99.307	99.869
0.0600	0.84739	0.00254	0.84945	0.00048	99.701	99.943
0.0700	0.83999	0.00109	0.84087	0.00021	99.870	99.975
0.0800	0.83287	0.00047	0.83325	0.00009	99.943	99.989
0.0900	0.82594	0.00021	0.82611	0.00004	99.975	99.995
0.1000	0.81915	0.00009	0.81922	0.00002	99.989	99.998

Table 3(e)

	K: 1.0				K̄: 300.0	
T	Q	Q̄	R	R̄	Q/(Q + Q̄) (× 100)	R/(R + R̄) (× 100)
0.0000	1.00000	1.00000	1.90000	0.10000	50.000	95.000
0.0035	0.93186	0.23196	1.12739	0.03643	80.069	96.870
0.0070	0.90603	0.07837	0.97049	0.01390	92.039	98.588
0.0105	0.89457	0.02920	0.91837	0.00540	96.839	99.415
0.0140	0.88846	0.01127	0.89761	0.00212	98.747	99.764
0.0175	0.88441	0.00442	0.88799	0.00084	99.503	99.906
0.0210	0.88117	0.00174	0.88258	0.00033	99.802	99.963
0.0245	0.87826	0.00069	0.87882	0.00013	99.921	99.985
0.0280	0.87549	0.00028	0.87571	0.00005	99.969	99.994
0.0315	0.87278	0.00011	0.87287	0.00002	99.987	99.998
0.0350	0.87011	0.00004	0.87014	0.00001	99.995	99.999

Table 4. (a) . . . (c) The reaction of racemic Q + $\bar{Q}$ (q = $\bar{q}$ = 1.0) with an equivalent amount of partially resolved racemate R + $\bar{R}$ (r = 1.1, $\bar{r}$ = 0.9, i.e. 10% E.E.) and different values of x = $\bar{k}$/k: (a) x = 3, (b) x = 100, (c) x = 300. Tables 4(a) . . . (c) and Fig. 3(a) . . . (c) are mutually complementary

Table 4(a)

	K: 1.0				$\bar{K}$: 3.0	
T	Q	$\bar{Q}$	R	$\bar{R}$	Q/(Q + $\bar{Q}$) (× 100)	R/(R + $\bar{R}$) (× 100)
0.0000	1.00000	1.00000	1.10000	0.90000	50.000	55.000
1.0000	0.21840	0.18264	0.22733	0.17371	54.459	56.685
2.0000	0.12649	0.09690	0.13017	0.09321	56.623	58.272
3.0000	0.09029	0.06475	0.09241	0.06264	58.236	59.599
4.0000	0.07080	0.04806	0.07221	0.04665	59.567	60.753
5.0000	0.05857	0.03789	0.05959	0.03686	60.721	61.781
6.0000	0.05015	0.03107	0.05094	0.03028	61.748	62.714
7.0000	0.04399	0.02619	0.04462	0.02557	62.680	63.571
8.0000	0.03928	0.02254	0.03979	0.02203	63.536	64.366
9.0000	0.03556	0.01972	0.03599	0.01928	64.330	65.109
10.0000	0.03253	0.01746	0.03290	0.01709	65.072	65.808

Table 4(b)

	K: 1.0				$\bar{K}$: 100.0	
T	Q	$\bar{Q}$	R	$\bar{R}$	Q/(Q + $\bar{Q}$) (× 100)	R/(R + $\bar{R}$) (× 100)
0.0000	1.00000	1.00000	1.10000	0.90000	50.000	55.000
0.0200	0.37658	0.28991	0.38774	0.27875	56.502	58.176
0.0400	0.24862	0.15578	0.25262	0.15178	61.478	62.467
0.0600	0.19403	0.09987	0.19604	0.09786	66.018	66.704
0.0800	0.16413	0.06966	0.16533	0.06846	70.205	70.716
0.1000	0.14550	0.05102	0.14628	0.05024	74.039	74.436
0.1200	0.13294	0.03856	0.13348	0.03802	77.514	77.829
0.1400	0.12401	0.02979	0.12440	0.02940	80.629	80.883
0.1600	0.11742	0.02338	0.11771	0.02309	83.394	83.601
0.1800	0.11242	0.01857	0.11264	0.01835	85.825	85.994

Table 4(c)

	K: 1.0				$\bar{K}$: 300.0	
T	Q	$\bar{Q}$	R	$\bar{R}$	Q/(Q + $\bar{Q}$) (× 100)	R/(R + $\bar{R}$) (× 100)
0.0000	1.00000	1.00000	1.10000	0.90000	50.000	55.000
0.0100	0.29891	0.20604	0.30512	0.19983	59.195	60.426
0.0200	0.19639	0.09967	0.19838	0.09769	66.334	67.004
0.0300	0.15639	0.05887	0.15732	0.05793	72.652	73.086
0.0400	0.13574	0.03800	0.13626	0.03747	78.129	78.431
0.0500	0.12354	0.02575	0.12386	0.02543	82.750	82.967
0.0600	0.11574	0.01798	0.11595	0.01777	86.552	86.711
0.0700	0.11050	0.01281	0.11065	0.01266	89.615	89.733
0.0800	0.10687	0.00924	0.10697	0.00914	92.041	92.128
0.0900	0.10428	0.00673	0.10435	0.00666	93.936	94.001
0.1000	0.10239	0.00494	0.10245	0.00488	95.400	95.449

strate that even a mixture of R and $\bar{R}$ with a slight excess of R is capable of reacting with racemates Q and $\bar{Q}$ to yield Q in any degree of optical purity, or enantiomer excess (E.E), resp., if x > 1. This may be of interest in connection with the origin of pure chiral compounds.

A similar approach can be applied to mixtures of two, or more non-enantiomeric chemical compounds. Accordingly, the present results indicate that the non-linear selectivity effects of independent parallel reactions can be used to obtain a pure chemical compound from a mixture of chemical analogs by reacting this mixture with a suitable reagent, which may also contain some similar compounds as impurities.

An application of this could be the purification of an L-α-amino acid that is contaminated by a small amount of D-enantiomer. A chiral reagent which would react preferentially with the D-α-amino-acid, could be employed in such a purification, even if it is not optically pure.

Numerical computations. Since an explicit solution of the non-linear system of differential equations could not be found, we computed a numerical approximation to the

exact solution by an explicit fourth-order Runge–Kutta algorithm.

The difference between a numerical solution (P_h, $\bar{P}_h$, Q_h, $\bar{Q}_h$), which corresponds to an integration step width h, and the exact solution (P, $\bar{P}$, Q, $\bar{Q}$) fulfils the following relation:

$$\|(P_h, \bar{P}_h, Q_h, \bar{Q}_h) - (P, \bar{P}, Q, \bar{Q})\| \leq C \cdot h^4 \qquad (13)$$

(where $\|P, \bar{P}, Q, \bar{Q}\| := \sqrt{P^2 + \bar{P}^2 + Q^2 + \bar{Q}^2}$).

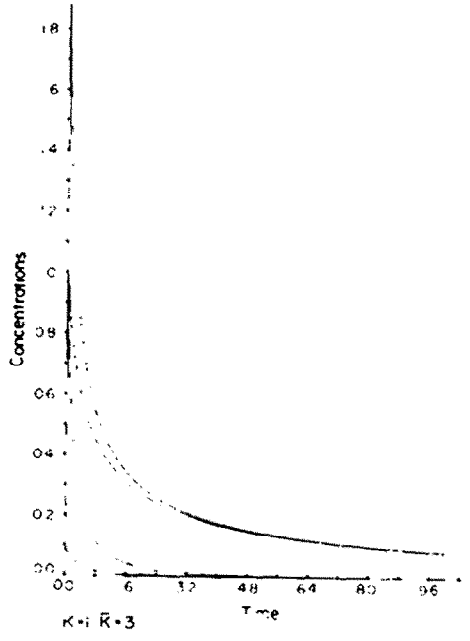


Fig. 2(a).

Fig. 2. (a) ... (e) The reaction of racemic $Q \rightleftarrows \bar{Q}$ ($q = \bar{q} = 1.0$) with an equivalent amount of partially resolved racemate $R \rightleftarrows \bar{R}$ ($r = 1.9$, $r = 0.1$, i.e. 90% EE) and different values of $x = \bar{k}/k$: (a) $x = 3$, (b) $x = 10$, (c) $x = 30$, (d) $x = 100$, (e) $x = 300$. Figure 2(a) ... (e) and Table 3(a) ... (e) are mutually complementary.

The constant C in (13) depends only on the integration interval [0, T] and on higher derivatives of the exact solution which, initially, is not known, but it is independent of the stepwidth h. To obtain an estimate of C, the stepwidth h_k, $h_k > h_{k+1}$, was gradually decreased until two successive numerical solutions (P_{h_k}, $\bar{P}_{h_k}$, Q_{h_k}, $\bar{Q}_{h_k}$) and ($P_{h_{k+1}}$, $\bar{P}_{h_{k+1}}$, $Q_{h_{k+1}}$, $\bar{Q}_{h_{k+1}}$) differed by not more than 10^{-4} (relative error). We found this to be satisfied for $h = 0.01$.

Numerical solutions for different rate constants k and $\bar{k}$ and initial concentrations P_0, $\bar{P}_0$, Q_0, $\bar{Q}_0$ were obtained. The concentrations p, $\bar{p}$, q, $\bar{q}$ as a function of time are listed in Table 3 and plotted in Fig. 2.

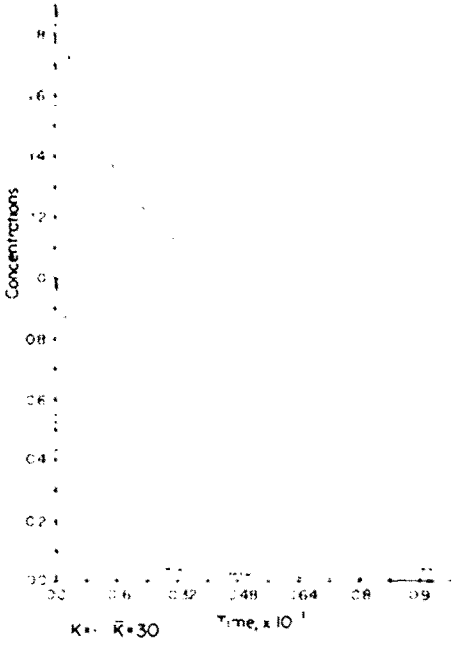


Fig. 2(c).

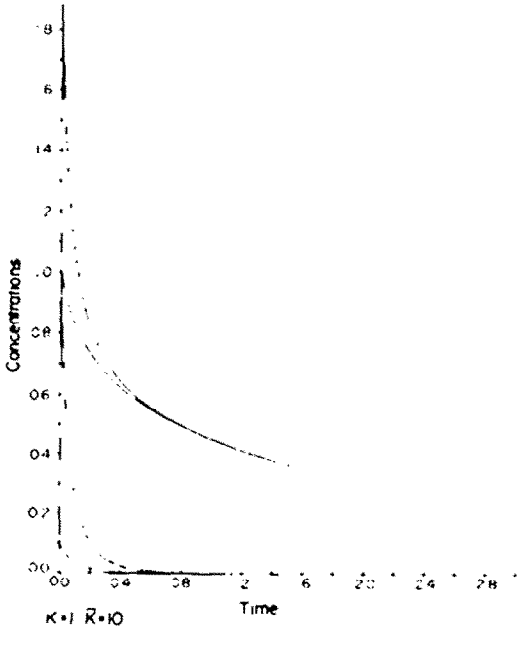


Fig. 2(b).

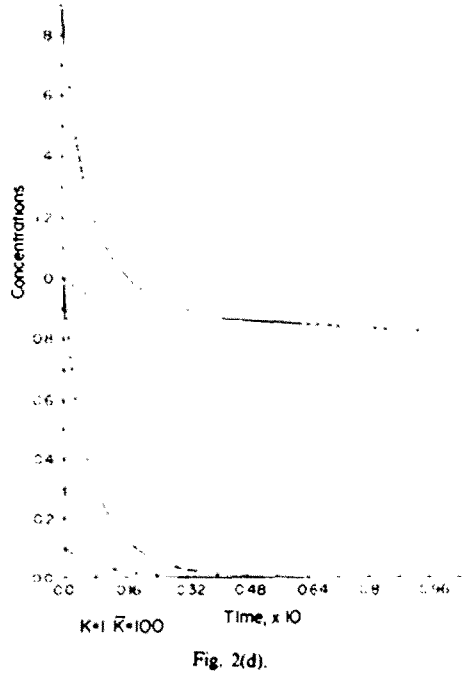


Fig. 2(d).

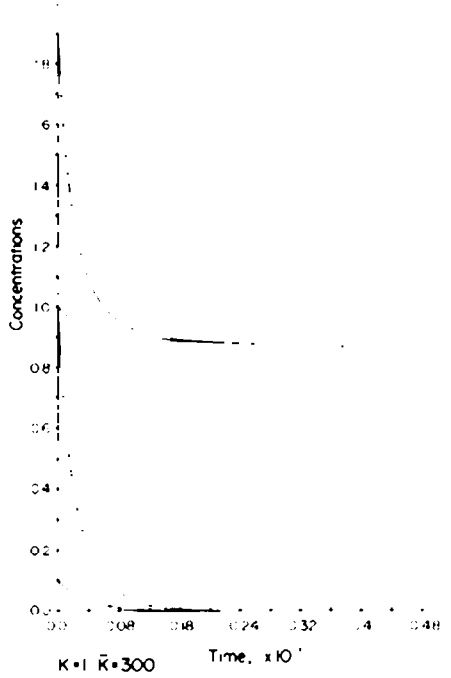


Fig. 2(e).

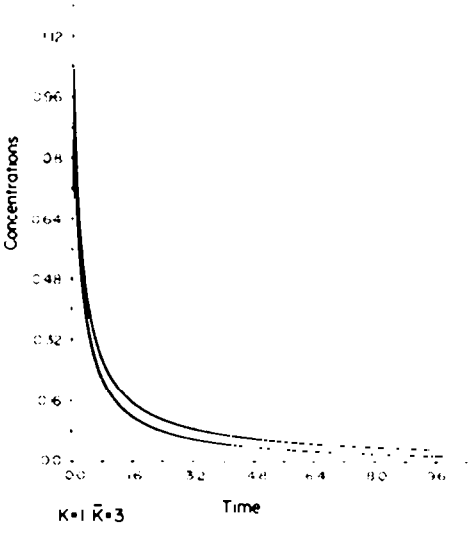


Fig. 3(a).

Fig. 3. (a) . . . (c) The reaction of racemic $Q + \bar{Q}$ ($q = \bar{q} = 1.0$) with an equivalent amount of partially resolved racemate $R + \bar{R}$ ($r = 1.1$, $\bar{r} = 0.1$, i.e. 10% EE) and different values of $x = k/\bar{k}$: (a) $x = 3$, (b) $x = 100$, (c) $x = 300$. Figure 3(a) . . . (c) and Table 4(a) . . . (c) are mutually complementary.

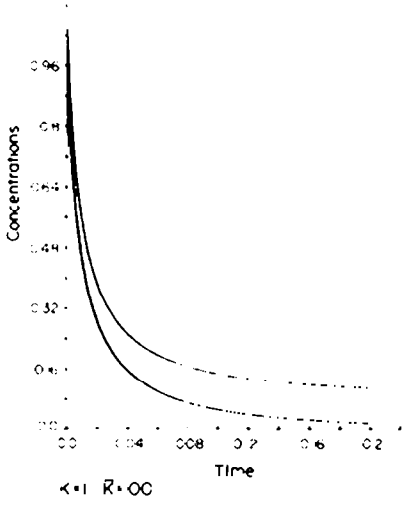


Fig. 3(b).

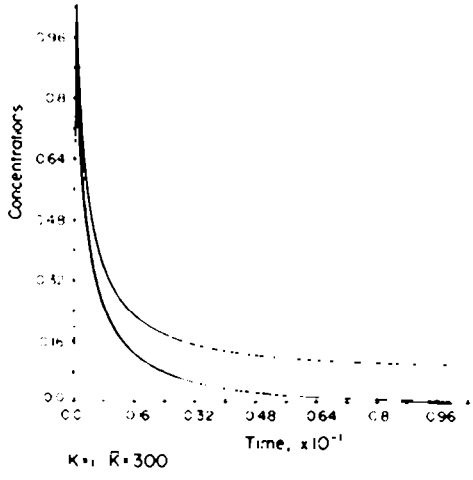


Fig. 3(c).

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[22]An equation of this form was derived by I. Ugi (1971/72), as an extension of the work presented in ref. 11 and incorporated in a publication which was submitted to *Theoret. Chem. Acta, Berlin*, and rejected, because it was not considered to be a contribution to theoretical chemistry.