138151-65-2; **8h**, 138151-66-3; **8i**, 106912-94-1; **8j**, 14845-77-3; **8k**, 138151-67-4; **10a** (R = Bu), 138151-68-5; **10b** (R = Ph), 138151-69-6; **10b** (R = *n*-Bu), 138151-70-9; 3-isopropoxy-4-methyl-3-cyclobutene-1,2-dione, 114094-69-8; 2-methyl-3-isopropoxy-4-hydroxy-2-cyclobutenone, 138151-71-0; dibenzylamine, 103-49-1; 3-methyl-4-(*N*,*N*-dibenzylamino)-3-cyclobutene-1,2-dione, 138151-72-1; 2-methyl-3-(*N*,*N*-dibenzylamino)-4-hydroxy-2-cyclobutenone, 138151-73-2; diisopropyl squarate, 138151-74-3; 3,4-di-*n*-butyl-3-cyclobutene-1,2-dione, 122967-65-1; 2,3-di-*n*-butyl-4-hydroxy-2-cyclobutenone, 138151-75-4; 3-isopropoxy-4-phenyl-3-cyclobutene-1,2-dione 2-ethylene acetal, 128242-44-4; 4-hydroxy-2-isopropoxy-4-methyl-3-phenyl-2-cyclobutenone ethylene acetal, 138151-76-5; 3-methyl-4-phenyl-3-cyclobutene-1,2-dione 2-ethylene acetal, 138151-77-6; 2-hydroxy-4-methyl-3-phenyl-3-cyclobutenone ethylene acetal, 138151-78-7; 2-hydroxy-4-methyl-3-phenyl-3-cyclobutenone, 138151-79-8; 3-isopropoxy-4-methyl-3-cyclobutene-1,2-dione 2-ethylene acetal, 128242-41-1; 4-methyl-3-phenyl-3-cyclobutene-1,2-dione 2-ethylene acetal, 129034-75-9; 4-hydroxy-3-methyl-2-phenyl-2-cyclobutenone, 138151-80-1; vinyltributyltin, 7486-35-3; (1-ethoxyethenyl)tributylstannane, 97674-02-7; phenyltrimethyltin, 934-56-5; 3-ethoxy-2-cyclobutenone, 4683-54-9; 4-ethoxy-4-(tri-*n*-butylstannyl)-3-buten-2-one, 138151-81-2; phenylacetylene, 536-74-3; 1-hexyne, 693-02-7; 2,3,6-tri-*n*-butylphenol, 138151-82-3.

Treating the Camphors with Potassium in Liquid Ammonia Leads to a Double Horeau Duplication

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Abstract: When potassium dissolves in solutions of the enantiomeric camphors *R*-**1** and *S*-**1**, variously enantioenriched camphors (**1**), and racemic camphor *RS*-**1** in liquid ammonia/THF at −77 °C, potassium alcoholates of the borneols *R*-**2** and *S*-**2** and isoborneols *R*-**3** and *S*-**3** plus equivalent amounts of the potassium enolates of *R*-**1** and *S*-**1**—enantiomeric, enantioenriched, and racemic—are produced by a transfer of a β-hydrogen from some **1**-derived unit to another [a ketyl disproportionation (hydrogen atom transfer)?]; the exact mechanism is still unknown. Hydrolysis gives enantiomeric, racemic, and enantioenriched **1–3**. The mole fractions and enantiomeric compositions (ec's) of **2** and **3** were determined and plotted against the ec's of the substrates **1**. The extremes of the resulting three curves are defined by the enantiomers *R*-**1** and *S*-**1** leading to about 1/1 mixtures of *R*-**2** and *R*-**3** and *S*-**2** and *S*-**3**, respectively, and the turning points by *RS*-**1** leading to a 9/1 mixture of *RS*-**2** and *RS*-**3**. The ec vs ec curve is close to linear in the case of **2** and strongly nonlinear in the case of **3**: from enantioenriched substrates **1**, one obtains isoborneols **3** with ec's that are strongly amplified with respect to the ec's of the substrates. Fitting the plots into a statistical kinetic model suggests (1) that **3** is formed via one homochiral process (involving units with the same chirality) and **2** via a combination of second homochiral process with a single heterochiral one (involving units with opposite chirality), (2) that the rate-determining steps in these processes are fourth order with respect to the substrates **1** (!), and (3) that all parallel steps have similar or identical rate constants. The homochiral process that leads to **3** amounts to a double Horeau duplication. Statistical oligomerization or condensation of enantioenriched monomers to short oligomers leads to homochiral oligomers with strongly amplified ec. (+)-Camphor *R*-**1** (ec 99.6%) and (−)-camphor *S*-**1** (ec 98.3%) from the chiral pool were not quite enantiopure.

1. Introduction

Exposure to alkali metals may be the oldest known method for transforming a ketone into the corresponding alcohol(s), and the camphors may be the oldest known organic chemicals.[1] There are many ways of doing these reductions[2] and one of the simplest—exposure to sodium suspended in hot toluene followed by hydrolysis—was applied by Baubigny[3a] to (+)-camphor *R*-**1**[4] as early as the 1860s, when both the structure and the functional group were still unknown. He nevertheless has already described the phenomenon we are concerned with here,[3a] and in the 1890s, the sodium/ethanol reduction of *R*-**1** was even carried out industrially.[3b] These particular procedures are called dissolving metal reductions and were thought to involve nascent hydrogen.[3a] A number of procedural variants are still in use today, and the theory behind them is of considerable interest: while they start out with one of the simplest and most basic reactions imaginable, reaction with an electron, what happens afterward is often complicated and still far from understood.

This paper is concerned with the extraordinarily complex sequence of chemical events that takes place when the camphors **1** are exposed to the blue solution of ammoniated electrons (e^-_{am}) and potassium ions that is formed when metallic potassium dissolves in liquid ammonia, and its starting point was the resolution of a minor controversy. Three groups had studied this reaction and one had come up with results quite different from those of the other two. Much later, we realized that the reason for this was that the enantiomers and the racemate behave differently.[5d] This was conclusive proof that a bimolecular step involving two camphor-derived units intervenes, but we had already found independent, equally conclusive evidence for such a step before

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[†] Deceased Aug 15, 1989.

[1] Almost everything has been tried with the camphors! See: (a) *Beilstein.* (b) Simonsen, J. L. *The Terpenes*, 2nd ed.; Cambridge University Press: Cambridge, U.K., 1949; Vol. 2, pp 349–367, 373–512. For example, when Wynberg and Feringa first systematically explored enantiomeric recognition and interaction, they studied the $LiAlH_4$ reduction of the camphors (ref 6a),[22] and Hoffmann and Laszlo chose representations of *R*-**1** to illustrate what the representations mean: (c) Hoffmann, R.; Laszlo, P. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1–16, cf. **1–14**.

[2] Reviews: House, H. O. *Modern Synthetic Reactions*, 2nd ed.; Benjamin: Menlo Park, CA, 1972; Chapter 3. Caine, D. *Org. React.* (*N. Y.*) **1976**, *23*, 1–258.

[3] (a) Baubigny, H. *Ann. Chim. Phys.* **1870**, [IV] *19*, 221–272. (b) Beckmann, E. *J. Prakt. Chem.* **1897**, *55*, 14–40. Beckmann, E. *Ber. Dtsch. Chem. Ges.* **1894**, *27*, 2348–2350.

[4] IUPAC rules: (1*R*,4*R*)-**1**, etc. For brevity, only the centers C(1) are specified and the locants and parentheses omitted throughout.

[5] (a) Rautenstrauch, V.; Geoffroy, M. *J. Am. Chem. Soc.* **1976**, *98*, 5035–5037. (b) Rautenstrauch, V.; Geoffroy, M. *J. Am. Chem. Soc.* **1977**, *99*, 6280–6286, 8373–8374. (c) Rautenstrauch, V.; Willhalm, B.; Thommen, W.; Burger, U. *Helv. Chim. Acta* **1981**, *64*, 2109–2137. (d) Rautenstrauch, V. *Helv. Chim. Acta* **1982**, *65*, 402–406. (e) Rautenstrauch, V. *Tetrahedron* **1988**, *44*, 1613–1618. (f) Rautenstrauch, V. *J. Chem. Soc., Chem. Commun.* **1986**, 1558–1560.

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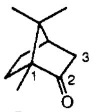
that[5b,c] and had also shown that it is suppressed when the reaction is carried out in the presence of ammonium ion.[5c] Therefore, the mechanism is then less complex—a double-electronation–protonation sequence, which is nevertheless also not fully understood[5f]—and we therefore proposed that this procedure is the best one to use preparatively.[5c]

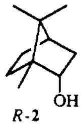
The special fascination of this chemistry is that it is old and has turned out to be modern. On looking more closely, we have uncovered an autocatalytic process, a strong amplification phenomenon, and asymmetric autocatalysis. These concepts are only now emerging[6] within that new paradigm[7] which is enantioselective synthesis. Our chemistry nicely illustrates these effects, but despite its apparent simplicity and hence model character, we still do not fully understand it.

2. Procedures and Effects

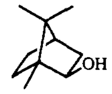
Coulombeau and Rassat[8] had added (*R*)-camphor *R*-**1** in diethyl ether solution, inversely, at once, to the blue solution (0.1 M) of 5 equiv of potassium in stirred liquid ammonia at reflux (−33.4 °C) with no other proton source present; after 30 min, the blue solution was quenched with ethanol to destroy the excess e^-_{am} and a hydrolytic workup was done. This led to a 40/60 mixture of (*R*)-borneol *R*-**2** and (*R*)-isoborneol *R*-**3** in close to quantitative yield. Murphy and Sullivan[9] had added 2.2 equiv of potassium normally, at once, to the solution of *R*-**1** (0.05 M) in liquid ammonia/diethyl ether, also at reflux and with no other proton source present; after 30 min, the solution was quenched with ammonium chloride and a hydrolytic workup was done. This had given practically the same result: a 42/58 mixture of *R*-**2** and *R*-**3** in 95% yield. Huffman and McWhorter[10a] had applied the Coulombeau-Rassat and Murphy-Sullivan procedures to *RS*-**1** and had obtained 82/18 and 84/16 mixtures of *RS*-**2** and *RS*-**3**, respectively, again practically the same result with both procedures, but a result that was different from the Coulombeau–Rassat and Murphy–Sullivan ones. They had also added *RS*-**1** in diethyl ether solution to a large excess of potassium solution (50 equiv) at much higher concentration (1.4 M) and had obtained the same result and determined yields of 84 and 95%. The discrepancy seemed inexplicable because it was not realized that different camphors were used and that they behave differently. These careful experiments had also established that all three procedures furnish exclusively the borneols **2** and isoborneols **3** (in particular, no pinacols[8–11] and no bornanes[9]) in virtually quantitative yield, the addition mode and the concentration of the e^-_{am} in the inverse addition mode not affecting the outcome,[12] and we had later reconfirmed this.[5c]



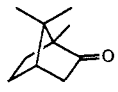
R-1
R-camphor



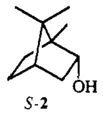
R-2
R-borneol



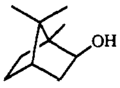
R-3
R-isoborneol



S-1



S-2



S-3

We had found that these procedures quickly (≤1 min) lead to 1/1 mixtures of potassium enolates and alcoholates,[5b–e] for example, to about 1 mol of the potassium enolate of *R*-**1** and 0.4 mol of the alcoholate of *R*-**2** plus 0.6 mol of the alcoholate of *R*-**3** from 2 mol of *R*-**1**. On further, extended exposure to the blue solution, the enolates formed in this first cycle are then recycled via protonation by the ammonia and eventually transformed completely into alcoholates as well, and this occurred in the Coulombeau–Rassat, Murphy–Sullivan, and Huffman experiments. We demonstrated the former point by applying the Coulombeau–Rassat procedure to *R*-**1** and *RS*-**1**, but roughly titrating until the blue color disappeared, and showed at the same time that the stereochemical outcomes in these first cycles are the same as when the enolates are converted as well:[5d] we found *R*-**2**/*R*-**3** = 40/60 and *RS*-**2**/*RS*-**3** = 85/15, plus about equivalent amounts of *R*-**1** and *RS*-**1** that were generated from the enolates. The fact that one can titrate and then immediately work up shows that the entire process is rapid.

In the present experiments, we added a small piece of potassium to the stirred solution of the camphors but used only 1 equiv or somewhat less (0.8–1 equiv, 0.3–0.4 mmol), at about −77 °C[13] (rather than at reflux) and in ammonia/THF (rather than ammonia/diethyl ether). A blue trail appeared in the wake of the dissolving potassium piece as it moved through the solution. The blue trails contained the e^-_{am} and potassium ions which quickly reacted with the camphors. A cloudy-white solution resulted when the metal was gone, which took about a minute. This was quenched with ammonium chloride and then worked up with water.

We had hoped that lowering the temperature—about as far as possible[13]—would increase the diastereoselectivity of the processes that lead to the alcoholates in the case of the racemate. This occurred and the weak diastereoselectivity in the case of the enantiomers essentially disappeared as well: *RS*-**2**/*RS*-**3** was about 90/10 and *R*-**2**/*R*-**3** = *S*-**2**/*S*-**3** close to 50/50. Both ratios are more extreme and therefore easier to analyze, and this is the main reason we investigated the phenomenon under these experimental conditions. Other reasons were that we had used the same procedure in our earlier work,[5c] that Huffman and Wallace had later used it on certain labeled camphors as well (section 8),[10b] and that we wanted to correlate all of the results. The normal addition mode was preferred because the dosage of the e^-_{am} is then more accurate—there is more time for side reactions when the blue solution is made first—but we knew that the addition mode does *not* affect the outcome (see above). Using just 1 equiv of potassium or, for good measure, somewhat less, has the advantage that all of the e^-_{am} react—one does not get a blue solution at the end—so that the quench does not liberate substrate from the enolate in the presence of e^-_{am} and ammonium ion; these could react by another mechanism[5c] before the e^-_{am} are quenched.

3. A Paradox?

We were at first convinced that a normal bimolecular step was responsible.[5d] Our results pointed to disproportionations of the ketyls, i.e., radical (anion) disproportionations, transfers of a hydrogen atom from one ketyl to the other,[5b–e,14] and this hypothesis had at first seemed to make perfect sense.[5d] The homochiral[15] disproportionations, of ketyls with the same chirality,

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[6] (a) Wynberg, H.; Feringa, B. *Tetrahedron* **1976**, *32*, 2831–2834. (b) Puchot, C.; Samuel, O.; Dunach, E.; Zhao, S.; Agami, C.; Kagan, H. B. *J. Am. Chem. Soc.* **1986**, *108*, 2353–2357. (c) Oguni, N.; Matsuda, Y.; Kaneko, T. *J. Am. Chem. Soc.* **1988**, *110*, 7877–7878. (d) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028–4036. Review: (e) Wynberg, H. *Chimia* **1989**, *43*, 150–152. For a review of diastereomeric interactions of enantiomers and a catalytic process involving a heterochiral dimer, see: (f) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49–69.

[7] Kuhn, T. S. *The Structure of Scientific Revolutions*, 2nd ed.; University of Chicago Press: Chicago, 1970.

[8] Coulombeau, A.; Rassat, A. *Chem. Commun.* **1968**, 1587–1589. Coulombeau, A.; Rassat, A. *Bull. Soc. Chim. Fr.* **1970**, 4399–4403.

[9] Murphy, W. S.; Sullivan, D. F. *J. Chem. Soc., Perkin Trans. 1* **1972**, 999–1003.

[10] (a) Huffman, J. W.; McWhorter, W. W. *J. Org. Chem.* **1979**, *44*, 594–599. (b) Huffman, J. W.; Wallace, R. H. *J. Am. Chem. Soc.* **1989**, *111*, 8691–8698.

[11] Pradhan, S. K.; Thakker, K. R.; McPhail, A. *Tetrahedron Lett.* **1987**, *28*, 1813–1816.

[12] A referee opined that this chemistry is extraordinarily sensitive to reaction conditions and gives a variety of products. This is not so in the present case, which is one reason why we studied it. The only sensitive points of this kind may be the $Y_{(R\text{-}3+S\text{-}3)}$ for and near the enantiomers (section 4; graph 1) and the scatter in the conversions, but the former were corrected by the regression analysis and the product compositions shown to be invariant with respect to conversion (section 5). State of the art capillary gas chromatography after hydrolysis detected *only* **1**–**3**. We ran the reactions under argon, but this is not necessary: Coulombeau and Rassat[8] and Huffman's group[10] had run them under air (and Murphy and Sullivan[9] under nitrogen).

[13] Ammonia freezes at −77.7 °C; acetone/CO_2 bath [−77 °C (Gordon, A. J.; Ford, R. A. *The Chemist's Companion*; Wiley: New York, 1972; p 451)]; THF as cosolvent.

[14] Reviews: (a) Huffman, J. W. *Acc. Chem. Res.* **1983**, *16*, 399–405. (b) Pradhan, S. K. *Tetrahedron* **1986**, *42*, 6351–6388. Pradhan takes another view; for comments, see: (c) Huffman, J. W.; Liao, W. P.; Wallace, R. H. *Tetrahedron Lett.* **1987**, *28*, 3315–3318, and ref 5e. A similar disproportionation takes place when ketones are exposed to sodium in toluene,[3a] to lithium in THF,[5a,b] to lithium, sodium, and potassium in THF with sonication,[10b] and to [K^+ 18-c-6] K^- in THF: (d) Jedlinski, Z.; Misiolek, A.; Glowkowski, W. *Synlett* **1990**, 213–214. Jedlinski, Z.; Misiolek, A.; Glowkowski, W.; Janeczek, H.; Wolinska, A. *Tetrahedron* **1990**, *46*, 3547–3558, and references cited therein.

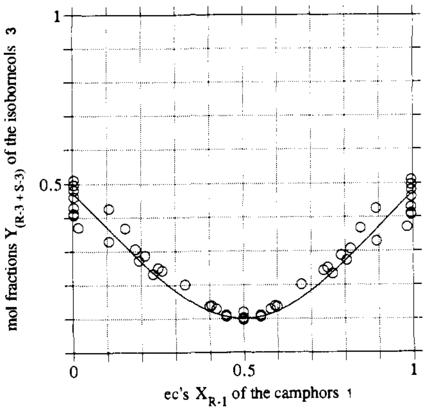

Figure 1. Graph 1.

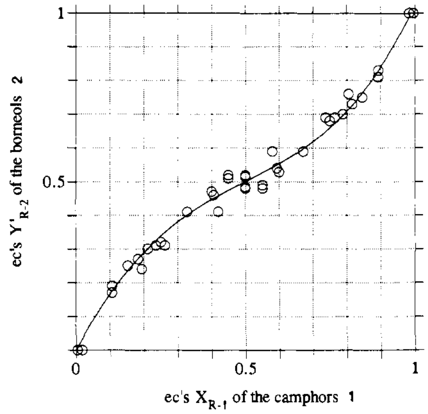

Figure 2. Graph 2.

and the heterochiral[15] ones, of ketyls with opposite chirality, would be different—the transition states would be diastereoisomers[5d,6]—and their diastereoselectivities, and in principle their rates, would therefore be different.

But the effect seemed much too big. Radical disproportionations are near diffusion-controlled or diffusion-controlled.[16] If our transfers were indeed radical disproportionations and also diffusion-controlled (section 7), then one would expect low selectivities, simply because every encounter would lead to a disproportionation. This conclusion was at first intuitive-qualitative but was later quantified (section 6). This then led to a paradox. The high selectivity for the racemate suggested that the heterochiral disproportionations *had to be* faster than the homochiral ones. Since the basic mechanism had to be the same, this meant that neither was diffusion-controlled. However, different rates would bring about mutual kinetic resolution, which was not observed (section 5), which suggested that the rates had to be similar or identical.

4. New Experiments

Following a suggestion by Rassat, we made up mixtures of *R*-**1** and *S*-**1** between the racemate and the pure enantiomers, treated these with potassium, and determined the proportions of the four alcohols obtained by hydrolysis. Such substrates have been termed enantiomerically enriched (enantioenriched for short[17a]) or scalemic;[17b] we will use the term scalemic.

These experiments became feasible because and when enantiomer separation (enantioseparation for short) by capillary gas chromatography became feasible.[18] It enabled us to measure the proportions of both enantiomeric pairs, *R*-**2**, *S*-**2** and *R*-**3**, *S*-**3**, in a single gas chromatographic analysis of the mixture obtained by hydrolysis. At the time, we could not separate the camphors *R*-**1** and *S*-**1** and this would not have sufficed (see below), but analysis of the alcohols turned out to be enough.

Our findings are presented in three graphs in which the three sets of experimental data that define the compositions of the alcohol mixtures are plotted against the enantiomeric compositions (ec's)[19] of the substrates **1**. To be commensurate, mole fractions $Y_{(R-3+S-3)}$ of the isoborneols **3** (plot 1) and ec's Y'_{R-2} and Y'_{R-3} (which are also mole fractions, plots 2 and 3) rather than enantiomeric excesses (ee's)[19] of the borneols **2** and isoborneols **3** are plotted against the ec's X_{R-1} of the substrates **1**, on the same scale, from 0 to 1. The scale (rather than a scale in percent) simplifies the regression analyses. $Y_{(R-3+S-3)}$, Y'_{R-2} and Y'_{R-3} are fully defined below.

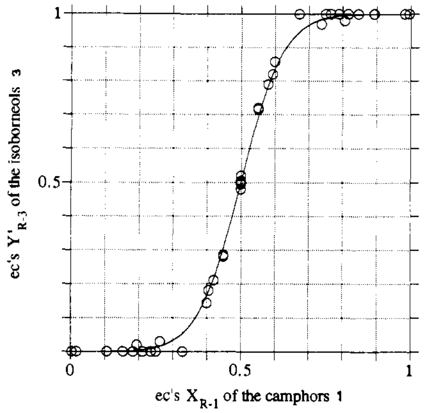

Figure 3. Graph 3.

What do these plots signify? We plot educt mole fractions against product mole fractions. We thus do competition experiments: two pairs of enantiomeric, homochiral processes and a single, so to say racemic, heterochiral process turn out to proceed in parallel (section 6). We find that all of the parallel rate constants are the same and derive the reaction orders of the rate-determining steps with respect to the substrate. This is developed further on: we first give the plots, then deal with the largely mathematical curve-fitting (section 6), and then discuss the kinetics (section 7).

Since gas chromatography without enantioseparation was still easier, more accurate, and much faster than gas chromatography with enantioseparation, the ratios of the borneols and isoborneols (*R*-**2** + *S*-**2**)/(*R*-**3** + *S*-**3**), without regard to their ec's, were determined first. Graph 1 shows the derived mole fractions of the isoborneols, $Y_{(R-3+S-3)} = (R\text{-}3 + S\text{-}3)/(R\text{-}2 + S\text{-}2 + R\text{-}3 + S\text{-}3)$, and a least-squares regression curve. The corresponding mole fractions for the borneols are $Y_{(R-2+S-2)} = 1 - Y_{(R-3+S-3)}$ (turn the graph upside down). This analysis also provided the proportions of the camphors (*R*-**1** + *S*-**1**) without regard to their ec's, and this permitted a check on the conversions, because we knew that about 1/1 mixtures of enolates and alcoholates are formed (section 2) and could therefore estimate the amount of enolates that was hydrolyzed back to camphors and hence the surplus, the

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(15) (a) Mislow, K.; Bickart, P. *Isr. J. Chem.* **1976/77**, *15*, 1. (b) Anet, F. A. L.; Miura, S. S.; Siegel, J.; Mislow, K. *J. Am. Chem. Soc.* **1983**, *105*, 1419–1426. (c) Damewood, J. R. *Chem. Eng. News* **1985**, Nov 4, 5.

(16) (a) Lehni, M.; Fischer, H. *Int. J. Chem. Kinet.* **1983**, *15*, 733–757, and references cited therein. (b) Benson, S. W. *Can. J. Chem.* **1983**, *61*, 881–887. (c) Wu, L. M.; Fischer, H. *Int. J. Chem. Kinet.* **1984**, *16*, 1111–1115. (d) Benson, S. W. *Acc. Chem. Res.* **1986**, *19*, 335–342. (e) Fischer, H.; Paul, H. *Acc. Chem. Res.* **1987**, *20*, 200–206.

(17) (a) Marshall, J. A. *Chem. Eng. News* **1990**, Nov 19, 47. (b) Heathcock, C. H. *Chem. Eng. News* **1991**, Feb 4, 3. (c) Eliel, E. L.; Wilen, S. H. *Chem. Eng. News* **1990**, Sept 10, 2. See also: Gal, J. *Chem. Eng. News* **1991**, May 20, 42. Castrillon, J. *Chem. Eng. News* **1991**, June 24, 94.

(18) (a) König, W. A. *The Practice of Enantiomer Separation by Capillary Gas Chromatography*; Hüthig: Heidelberg, 1987. (b) Allenmark, S. G. *Chromatographic Enantioseparation: Methods and Applications*; Ellis Horwood: Chichester, U.K., 1988. (c) Schurig, V.; Bürkle, W. *J. Am. Chem. Soc.* **1982**, *104*, 7573–7580. (d) Schurig, V.; Nowotny, H. P. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 939–957. Separation of *R*-**1** and *S*-**1**: (e) König, W. A.; Krebber, R.; Evers, P.; Bruhn, G. *J. High Resolut. Chromatogr.* **1990**, *13*, 328–332.

(19) ec = *R*-**1**/(*R*-**1** + *S*-**1**), ee = (*R*-**1** − *S*-**1**)/(*R*-**1** + *S*-**1**), where *R*-**1** is the major enantiomer.

unreacted camphors. We do not show these proportions because they are of no use without the corresponding ec's, i.e., the ec's of the camphors regenerated from the enolates and the ec's of the unreacted camphors. It would have been necessary to separate the camphors and enolates, to then convert the latter into camphors, and to measure the ec's of each, but we could not measure the ec's to begin with.

Graph 1 provides an entire curve of which only the three points for the enantiomers and the racemate had been known. Obviously, we also knew the ec's that correspond to these particular points, but the ec's that correspond to all of the other points in graph 1 were unknown at this stage. The regression gave $Y_{R\text{-}2} = Y_{S\text{-}2} = 0.53$ and $Y_{R\text{-}3} = Y_{S\text{-}3} = 0.47$ for the enantiomers and $Y_{RS\text{-}2} = 0.90$ and $Y_{RS\text{-}3} = 0.10$ for the racemate. These Y are specific values of the $Y_{(R\text{-}2+S\text{-}2)}$ and $Y_{(R\text{-}3+S\text{-}3)}$ above and are more accurate than those we had before (section 2; about 50, 50, 90, and 10%).

The scalemic substrates were made up by mixing *R*-**1** and *S*-**1**, or *R*-**1** and *RS*-**1**, and more experiments were done with *R*-**1**-rich mixtures, in the right halves of the graphs. However, every experimental point was taken to generate two mirror image points ($x' = 1 - x$; $y' = y$). This is justified because the curve must have this symmetry and the regression curve must reproduce it. The symmetries here and below actually helped in arriving at regression curves that were chemically and kinetically meaningful. The error in the weighing in making up the scalemic substrates is negligible.

The biggest scatter in graph 1 was near the enantiomerically pure[15c] (enantiopure for short[17c]) substrates. For each of these, we have nine points, and we have seven for the racemate. For the former, six of the nine points are scattered *below* the regression curve, while the points for the racemate all lie close together and fit well.[20] The accuracy was much better than the scatter, $\leq\pm\sim0.001$ (0–1.000 scale).[21a]

Next, the ec's $Y'_{R\text{-}2} = R\text{-}\mathbf{2}/(R\text{-}\mathbf{2} + S\text{-}\mathbf{2})$ of the borneols **2** and the ec's $Y'_{R\text{-}3} = R\text{-}\mathbf{3}/(R\text{-}\mathbf{3} + S\text{-}\mathbf{3})$ of the isoborneols **3** were determined by capillary gas chromatography using nickel bis[(1*R*)-3-(heptafluorobutyryl)camphorate][18c] in OV 101 as the stationary phase, and graphs 2 and 3 show these together with least-squares regression curves. The curves indicate how much *R*-**2** and *R*-**3** there was. The corresponding curves for *S*-**2** and *S*-**3** are mirror images of the curves shown ($Y'_{S\text{-}2} = 1 - Y'_{R\text{-}2}$, $Y'_{S\text{-}3} = 1 - Y'_{R\text{-}3}$), are thus equivalent, and are omitted for clarity. Every experimental point was again taken to generate two points, but the symmetry is different ($x' = 1 - x$; $y' = 1 - y$) from that in graph 1. One analysis (that took about 70 min) of the crude hydrolysate provided both ec's, in fact, the proportions of all four alcohols and thus the above $Y_{(R\text{-}3+S\text{-}3)}$ as well, but much less accurately (see below).[21] It so happens that this analytical artifact of measuring separately the mole fractions $Y_{(R\text{-}3+S\text{-}3)}$ and the ec's Y' provides the data in a way that is convenient for interpretation, but regardless of the analytical procedure (two analyses or one) and of how the data are presented, we have these three observations, $Y_{(R\text{-}3+S\text{-}3)}$ and the two ec's Y', and they are *independent*.

The curves are strinkingly different. That in graph 2 is slightly mirror-S-shaped, so that the ec's of the substrates **1** and the borneols **2** almost correspond to each other; strict correspondence would result in a diagonal. The curve in graph 3 is S- or ogive-shaped and shows a strong amplification phenomenon: for ec's $X_{R\text{-}1}$ of the substrates below about 0.2 and above about 0.8, close to enantiopure isoborneols *S*-**3** and *R*-**3**, respectively, are produced. Kagan and co-workers[6b] first systematically analyzed phenomena of this kind in the context of asymmetric synthesis, and in their terms, we have a nearly linear effect in graph 2 and a strongly nonlinear one in graph 3; a truly linear effect would give the diagonal.

Progress in gas chromatographic enantioseparation has been rapid,[18] and the analyses in graphs 2 and 3, which were made early in 1989, are probably already outdated. The separations were satisfactory, but we did not get base-line separations. The accuracy was verified, and the peaks of the four alcohols were identified by the experiments with the enantiomeric and racemic camphors and by analyzing test mixtures made by $LiAlH_4$ reduction[22] of camphors with ec's $X_{R\text{-}1}$ of 90 and 96%. The analytical errors in the ec's $Y'_{R\text{-}2}$ and $Y'_{R\text{-}3}$ measured for the test samples *and* the racemate[23] were ± about 0.02–0.03 (0–1.00 scale).[21b]

As already mentioned, *R*-**1** and *S*-**1** were not separated on the nickel heptafluorobutyrylcamphorate column. Our seeing single borneol **2** peaks in the appropriate experiments (graph 2) with the camphors so far referred to as enantiomeric and enantiopure indicated that their ec's were $\geq\sim98\%$, and our seeing double close to 50/50 borneol **2** and isoborneol **3** peaks in the experiments with the camphor so far referred to as racemic that it's ec was 50 ± 2–3%. Since the latter camphor had to be synthetic, it had to be truly (but not perfectly[15a]) racemic, but we did not know whether our *R*-**1** and *S*-**1** were really enantiopure. We used these three samples as such and for weighing in the scalemic camphors.

In the meantime, enantioseparation of the camphors became possible,[18d,e] and early in 1991, we therefore verified at least the ec's of our three camphors on an octakis(3-*O*-butyryl-2,6-di-*O*-pentyl)-γ-cyclodextrin column and found 50.1% for *RS*-**1**, 99.6% for *R*-**1**, and 98.3% for *S*-**1**.[24] We now had base-line separations and the analytical error was $\leq\pm\sim0.1$ (0–100.0 scale).[21c] Although graphs 1–3 were practically unchanged when corrections for these ec's of *R*-**1** and *S*-**1** were made, we did make the corrections, and $Y_{R\text{-}2} = Y_{S\text{-}2} = 0.53$ and $Y_{R\text{-}3} = Y_{S\text{-}3} = 0.47$ are thus extrapolated to substrate ec's of 100%.

5. Mutual Kinetic Resolution

One key parameter, conversion, has not been discussed so far. We began with experiments in which we added about 0.8–1 equiv of potassium, and this gave conversions between 50 and 90%, which were estimated as indicated under section 4. This scatter[12] in the conversions is probably due to the extent of adventitious side reactions that the e^-_{am} undergo, varying somewhat from run to run. The main such side reaction is that leading to potassium amide and dihydrogen. Also, we did not weigh the potassium any too accurately. We did not mind the scatter and the inaccurate weighing and simply tried first whether we could separate the three enantiomeric pairs, then improved the separations of the two alcohol pairs that we could separate, then tested them, and finally added more points to further define the curves that were emerging.

However, mutual kinetic resolution[25] would occur if the intrinsic rates of the hetero- and homochiral processes were different. For example, if the heterochiral disproportionations were indeed faster than the homochiral ones (section 3), then they would produce racemic alcoholates from scalemic substrates *more* rapidly than

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[20] In the fourth-order model of section 6, the homochiral processes are statistically disfavored with respect to the heterochiral ones. It could therefore be that the homochiral processes are more susceptible to competition by adventitious side reactions than the heterochiral ones, and this may manifest itself in graph 1: runs in the middle of graph 1 could be inherently more reproducible than runs at right and left.

[21] I.e., for example, (a) $Y_{(R\text{-}3+S\text{-}3)}$ was measured to be 0.510 $\pm\leq\sim0.001$ (0–1.000 scale, or 51.0 $\pm\leq\sim0.1\%$) on the achiral column, (b) the ec $Y'_{R\text{-}2}$ of *RS*-**2** to be 0.49 ± ~0.02–0.03 (0–1.00 scale, or 49 ± ~2–3%) on the nickel heptafluorobutyrylcamphorate column, and (c) the ec $X_{R\text{-}1}$ of *RS*-**1** to be 0.501 $\pm\leq\sim0.001$ (0–1.000 scale, or 50.1 $\pm\leq\sim0.1\%$) on the cyclodextrin column.

[22] The ec's of these camphors and the alcohols made from them by $LiAlH_4$ reduction must be closely similar: there are enantiomeric recognition and antipodal interaction effects,[6a] but they are weak and can be neglected.

[23] We are certain that the racemate is truly racemic and the points for the racemate were therefore also doubled in the graphs ($y' = 1 - y$).

[24] The ec's of *R*-**1** and *S*-**1** came as something of a surprise because the camphors are often-used members of the chiral pool,[1] for example, in the preparation of resolving agents (Wilen, S. H. *Top. Stereochem.* **1971**, *6*, 107–176. Wilen, S. H. *Tables of Resolving Agents and Optical Resolutions*; Eliel, E. L., Ed.; University of Notre Dame Press: Notre Dame, IN, 1972. Wilen, S. H.; Collet, A.; Jacques, J. *Tetrahedron* **1977**, *33*, 2725–2736. Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates, and Resolutions*; Wiley: New York, 1981), shift reagents (Gaudemer, A. In *Stereochemistry: Fundamentals and Methods*; Kagan, H. B., Ed.; Thieme: Stuttgart, 1977; Vol. I, pp 134–136), and auxiliaries (Oppolzer, W. *Pure Appl. Chem.* **1990**, *62*, 1241–1250) or as starting materials in numerous syntheses (Money, T. *Nat. Prod. Rep.* **1985**, *2*, 253–289. Money, T. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1989; Vol. IV). Nowhere have we found ec's and it may often have been assumed that they are enantiopure (for instance: Gerlach, H. *Helv. Chim. Acta* **1968**, *51*, 1587–1593). We have analyzed further samples which are all not quite enantiopure and will report on this elsewhere.

[25] Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249–330.

the homochiral disproportionations would produce alcoholates with increased ec's. Consequently, the ec's of substrate and products would continuously change as conversion progresses (section 6). Such systems have complex kinetics,[25,26] but in the present context, the essential conclusion was simply that one would then *not* expect smooth curves for variable conversions. Our curves instead suggested that our data were invariant with respect to conversion and thus that there was no mutual kinetic resolution.

This mutual resolution can be diagnosed by monitoring the ec's of the substrate and the products as conversion progresses; we monitored only the ec's of the alcohols **2** and **3** and thus of only half, but the essential half, of the products (section 4). Because our reactions are very rapid (section 7), we could also not monitor individual runs as conversion progressed; instead, we did separate runs in which we lowered the conversions by adding less potassium.

To confirm the invariance of our data with respect to conversion, we checked whether the initial alcohol compositions, *at very low conversion*—about 1%, using only about 0.01 equiv of potassium—when the substrate and the products would be practically unchanged by mutual kinetic resolution, were the same as at the standard high conversions. Before that, we did the same about 1% conversions experiments with the racemate and one enantiomer. The resulting $Y_{RS\text{-}3}$ and $Y_{R\text{-}3}$ nearly fell onto the regression curve in graph 1 (these points are marked in Table I). These control experiments provided information as to whether the mechanism is the same at low and high conversion, and the unchanged $Y_{R\text{-}3}$ and $Y_{RS\text{-}3}$ suggest that it is. We then did the same about 1% conversion experiments with two scalemic samples, with ec's $X_{R\text{-}1}$ of 60 and 85%. The resulting points in graphs 1–3 (also marked in Table I) all fitted well into the high-conversion points. We also did two experiments with the same sample with an ec $X_{R\text{-}1}$ of 55% using once 0.17 and once 0.80 equiv of potassium, and the resulting points were very close and again fitted well. If there were mutual kinetic resolution, then we should not see it at low conversion, but see it at high conversion: the results should be different. The results are the same: we conclude that no mutual kinetic resolution occurs and that graph 3 instead shows a different kind of kinetic resolution, which is indeed invariant with respect to conversion.

Obtaining accurate data for such low conversions was possible because we could again use capillary gas chromatography and a very sensitive (flame ionization) detector, but the experiments were analytically and experimentally more demanding. Obviously, we had to use the same procedure as in the high-conversion runs, but handling and weighing about $^1/_{100}$ the amount of potassium in the same manner as in the high-conversion runs was impossible. We therefore instead scaled up the entire experiments—using much more ammonia/THF and camphors—and added only somewhat less potassium than in the high-conversion runs. The camphors contained minute traces of the alcohols **2** and **3**,[10b] which falsified the results, and we therefore purified them rigorously. The nickel heptafluorobutyrylcamphorate column was overloaded by the enormous amounts of unreacted substrate when we injected enough of the mixtures trying to see the peaks of the traces of **2** and **3** that were formed directly. It was therefore necessary to remove some of the substrate, and this was done by standard preparative gas chromatography using an achiral phase. Since this can bring about enantioseparation,[27] samples still containing 75–90% substrate plus the entirely unseparated alcohol mixtures were collected, which we could analyze.

6. Curve Fitting

We were led to do these experiments by the disproportionation hypothesis, because the disproportionations proceeding at similar or identical, perhaps diffusion-controlled, rates would resemble Horeau's duplications.[25,28] Finding that they did would have strengthened the hypothesis and somehow resolved the paradox of section 3, and finding that they did not would have disproved it. They did not, but a closely related and nevertheless completely unexpected scheme was found that fits all of the data and resolves the paradox.

Horeau and co-workers[28a] had shown that chemical "duplication" of a scalemic substrate—for example, by making the two diastereoisomeric carbonate diesters from a scalemic alcohol—*separation* of the homochiral (*RR*, *SS*), chiral, scalemic "dimer" and the heterochiral, achiral (*RS*) meso dimer, and regeneration of the "monomer" from the homochiral dimer provide a monomer with amplified ec, without recourse to an external resolving agent. This is so because the substrate itself functions as the resolving agent, provided it is scalemic. Making the heterochiral meso dimer amounts to removal of racemic substrate from the original substrate (cleaving the meso dimer gives racemic substrate). Cleavage of the homochiral dimer provides substrate with correspondingly increased ec. The rate constants for the homo- and heterochiral duplications in Horeau's scheme are identical. Consequently, the homo- and heterochiral duplications produce the dimers in *unequal amounts* (see below) but at all times *jointly* remove substrate with the original ec, so that the ec of the substrate does *not* change as the duplication progresses. This is a kinetic resolution at the level of the products but not at the level of the substrates, and it is invariant with respect to conversion. Duplications in which the two rate constants are different of course also work, but the ec's of the substrate and the chiral dimer then change as the duplication progresses. This is then a mutual kinetic resolution, and the amplification is stronger and more efficient the more the heterochiral duplication is favored.[25] The heterochiral duplication then removes the minor enantiomer early on, and the homochiral duplication can simply be stopped when it is gone; the remaining monomer is enantiopure. The absence of mutual kinetic resolution in our case suggested a Horeau-like situation.

In Horeau's case, the "dimers" are diastereoisomers. In ours, the transition states of the homo- and heterochiral disproportionations would be diastereoisomers and the resulting alcohols **2** and **3** likewise. The products that would result from the two processes would nevertheless *not* be the same—except in the case of the racemate—because the heterochiral disproportionations would lead to racemic **2** and **3** and the homochiral ones to scalemic **2** and **3** with increased ec's, in unequal amounts—even if the diastereoselectivities (ratios **2**/**3**) were the same, which they could only be by accident. The alcoholates of the racemic and scalemic **2** and **3** would be generated side by side, but by determining the proportions of the four components—the two enantiomeric pairs—in the resulting mixture of alcoholates or alcohols, one could in principle identify the two pathways and determine their diastereoselectivities. One can do this for a few scalemic substrates, but the best way is to look at the *entire* ec range (the two scalemic ranges, the enantiomers, and the racemate) and to then model the resulting curves.

Identifying and fitting the curves were simplified by the fact that there was practically no diastereoselectivity in the homochiral processes—this we saw with the enantiomers—and high overall diastereoselectivity with the racemate where the homo- and heterochiral processes proceed side by side. A good approximation was therefore to assume that the heterochiral, "racemic" processes were completely diastereoselective, in other words, that there was in fact only a single heterochiral, racemic process that led to racemic borneol *RS*-**2** as outlined above, and that the homochiral processes were completely unselective, in other words, that there were two homochiral processes—each with two enantiomeric

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(26) Brandt, J.; Jochum, C.; Ugi, I.; Jochum, P. *Tetrahedron* **1977**, *33*, 1353–1363.

(27) Cundy, K. C.; Crooks, P. A. *J. Chromatogr.* **1983**, *281*, 17–33. Charles, R.; Gil-Av, E. *J. Chromatogr.* **1984**, *298*, 516–520. Tsai, W. L.; Hermann, K.; Hug, E.; Rohde, B.; Dreiding, A. S. *Helv. Chim. Acta* **1985**, *68*, 2238–2243. Matusch, R.; Coors, C. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 626–627.

(28) (a) Vigneron, J. P.; Dhaenens, M.; Horeau, A. *Tetrahedron* **1973**, *29*, 1055–1059. See also: (b) Marty, W.; Pasquier, M. L.; Gampp, H. *Helv. Chim. Acta* **1987**, *70*, 1774–1785. (c) Feringa, B. L.; Smaardijk, A.; Wynberg, H. *J. Am. Chem. Soc.* **1985**, *107*, 4798–4799. The principle was already conceived and tested but not yet quantified in 1936: (d) Langenbeck, W.; Triem, G. *Z. Phys. Chem. Abt. A* **1936**, *177*, 401–408. Added in proof: Wang, X. *Tetrahedron Lett.* **1991**, *32*, 3651–3654. Welch, C. J. *Tetrahedron: Asymmetry* **1991**, *2*, 1127–1132.

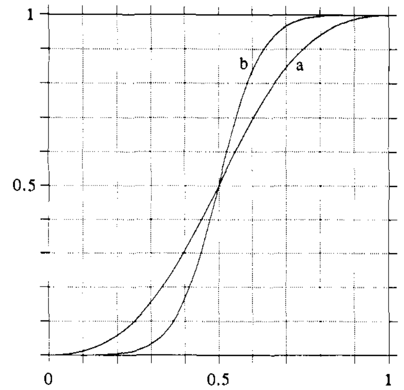

Figure 4. Graph 4: modeling the ec's of the isoborneols **3**. $y = x^n/[x^n + (1 - x)^n]$ (a) $n = 2$; (b) $n = 4$.

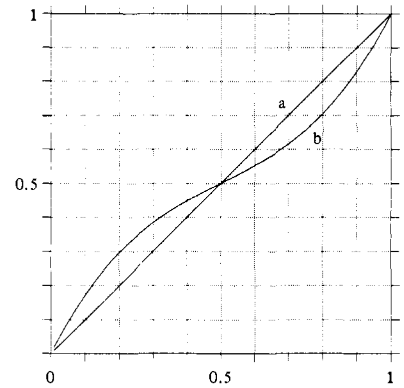

Figure 5. Graph 5: modeling the ec's of the borneols **2**. (a) $y = x$; (b) $y = x^4 + 2x^3(1 - x) + 3x^2(1 - x)^2 + 2x(1 - x)^3$.

versions—that provided 1/1 mixtures of **2** and **3** as outlined above. These assumptions meant that the isoborneols **3** were *only* produced by one of the homochiral processes and the borneols **2** by the other homochiral *and* the heterochiral processes. Therefore, modeling the enantiomeric homochiral processes that lead to the enantiomeric isoborneols **3**, thus the ec's $Y'_{R\text{-}3}$ (graph 3, or $Y'_{S\text{-}3}$, which is equivalent), was the most direct and telling test.

If the mole fractions of *R*-**1** and *S*-**1** in the substrates are respectively x and $(1 - x)$, then, following Horeau's analysis,[28a] the amounts of the isoborneols *R*-**3** and *S*-**3** formed would be given by x^2 and $(1 - x)^2$, respectively, and the ec's $Y'_{R\text{-}3}$ by

$$Y'_{R\text{-}3} = R\text{-}\mathbf{3}/(R\text{-}\mathbf{3} + S\text{-}\mathbf{3}) = x^2/[x^2 + (1 - x)^2] \quad (1)$$

Plotting this function gave curve a in graph 4 (Figure 4) which characterizes all Horeau duplications.[29] It resembles, but does not fit, the experimental curve in graph 3. However, the resemblance suggested that we were on the right track and that eq 1 only needed to be modified somehow. Larger exponents give more extreme S-curves (section 11) and we found that the function

$$Y'_{R\text{-}3} = R\text{-}\mathbf{3}/(R\text{-}\mathbf{3} + S\text{-}\mathbf{3}) = x^4/[x^4 + (1 - x)^4] \quad (2)$$

plotted as curve b in graph 4, gives a *perfect* fit. The regression curve in graph 3 is a least-squares fit for eq 2, and the correlation coefficient r is 0.999.

We made the fits in graphs 1–3 with a personal computer[30] but were lucky in that the isoborneols **3** are indeed only produced by one of the homochiral processes and that eq 2 is mathematically simple and easily arrived at starting from eq 1, eq 1 being in turn derived from a simple chemical/kinetic model. This was the essential clue to the puzzle, and it suggested that the rate-determining step in the homochiral processes that lead exclusively to the isoborneols **3** are fourth order (!) with respect to the substrate and not second order as in the original model.

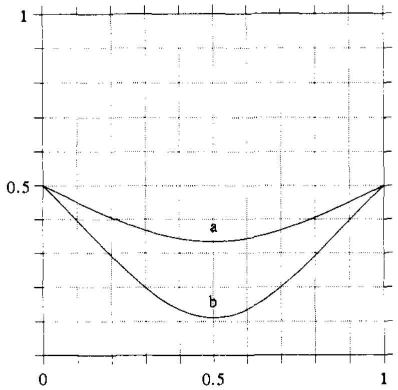

Figure 6. Graph 6: modeling the mole fractions of the isoborneols (*R*-**3** + *S*-**3**). $y = [x^n + (1 - x)^n]/[1 + x^n + (1 - x)^n]$ (a) $n = 2$; (b) $n = 4$.

This clue then also led to an equation that reproduced the ec's of the borneols **2** (graph 2) and was consistent with eq 2.

The borneols **2** are formed by the second homochiral and the heterochiral processes. We found that the total of all of the borneols **2** is approximately given by a binomial distribution

$$[x + (1 - x)]^4 = x^4 + 4x^3(1 - x) + 6x^2(1 - x)^2 + 4x(1 - x)^3 + (1 - x)^4$$

because one can then derive that the amounts of *R*-**2** and *S*-**2** formed via the homochiral processes are given by x^4 and $(1 - x)^4$, respectively, exactly as the amounts of the isoborneols **3**, the amounts of *RS*-**2** formed via the heterochiral processes by $4x^3(1 - x) + 6x^2(1 - x)^2 + 4x(1 - x)^3$, hence the amount of *R*-**2** formed by the heterochiral process by half that heterochiral term, $2x^3(1 - x) + 3x^2(1 - x)^2 + 2x(1 - x)^3$, and hence the total amount of *R*-**2** by $x^4 + 2x^3(1 - x) + 3x^2(1 - x)^2 + 2x(1 - x)^3$. This expression already defines the ec's $Y'_{R\text{-}2} = R\text{-}\mathbf{2}/(R\text{-}\mathbf{2} + S\text{-}\mathbf{2})$, because the denominator here is the entire binomial above (=1), thus

$$Y'_{R\text{-}2} = x^4 + 2x^3(1 - x) + 3x^2(1 - x)^2 + 2x(1 - x)^3 \quad (3)$$

Plotting eq 3 gave curve b in graph 5, which already gives an excellent fit with the experimental points in graph 2. The regression curve in graph 2 is a least-squares fit for the equation

$$y = c_1x^4 + c_2x^3(1 - x) + c_3x^2(1 - x)^2 + c_2x(1- x)^3$$

and we found $c_1 = 1.027$, $c_2 = 1.891$, $c_3 = 3.207$, and $r = 0.995$. While c_1 is nearly unity, c_2 is only close to 2 and c_3 only close to 3. This presumably reflects the fact that the two homochiral processes do not produce exactly 1/1 mixtures of **2** and **3**. It made sense that the borneols **2** corresponding to the term $6x^2(1 - x)^2$ are racemates, but we had to assume that the terms $4x^3(1 - x)$ and $4x(1 - x)^3$ also correspond to racemates.

The second-order counterpart is a binomial distribution

$$[x + (1 - x)]^2 = x^2 + 2x(1 - x) + (1 - x)^2$$

for the total of all of the borneols **2** and the ec's derived therefrom are simply

$$Y'_{R\text{-}2} = x^2 + x(1 - x) = x \quad (4)$$

Here the ec's $Y'_{R\text{-}2}$ would correspond exactly to the ec's of the camphors: a linear effect (diagonal a in graph 5).

The same fourth-order model also directly provided a consistent equation that closely reproduces the curve in graph 1. The mole fractions of the isoborneols $Y_{(R\text{-}3+S\text{-}3)}$ are given by

$$Y_{(R\text{-}3+S\text{-}3)} = (R\text{-}\mathbf{3} + S\text{-}\mathbf{3})/(R\text{-}\mathbf{2} + S\text{-}\mathbf{2} + R\text{-}\mathbf{3} + S\text{-}\mathbf{3}) = [x^4 + (1 - x)^4]/[1 + x^4 + (1 - x)^4] \quad (5)$$

(1 = binomial above). Plotting eq 5 gave curve b in graph 6, and

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(29) For the corresponding ee vs ee plots for dimerization and trimerization, see: (a) ref 25, p 279. (b) Grassi, M.; Di Silvestro, G.; Farina, M. *Tetrahedron* **1985**, *41*, 177–181. The corresponding eq are less transparent than the eq for ec's.

(30) Macintosh, data analysis (general curve fits) and graphics with KaleidaGraph.

the fit with the experimental points is already satisfactory. The regression curve in graph 1 is a least-squares fit for the equation

$$y = c_4[x^4 + (1 - x)^4]/[c_5 + c_4(x^4 + (1 - x)^4)]$$

and we found $c_4 = 2.219$, $c_5 = 2.472$ ($c_5/c_4 = 1.114$), and $r = 0.970$. That c_4 is only close to c_5, (c_5/c_4 only close to unity) presumably again reflects the fact that the homochiral processes do not produce exactly 1/1 mixtures. The regression curve gives $Y_{R\text{-}2} = Y_{S\text{-}2} = 0.53$ and $Y_{R\text{-}3} = Y_{S\text{-}3} = 0.47$ for the enantiomers and $Y_{RS\text{-}2} = 0.90$ and $Y_{RS\text{-}3} = 0.10$ for the racemate, while eq 5 gives $Y_{R\text{-}2} = Y_{S\text{-}2} = Y_{R\text{-}3} = Y_{S\text{-}3} = 0.50$ and $Y_{RS\text{-}2} = 0.89$ and $Y_{RS\text{-}3} = 0.11$.

In the analogous second-order model

$$Y_{(R\text{-}3+S\text{-}3)} = [x^2 + (1 - x)^2]/[1 + x^2 + (1 - x)^2] \qquad (6)$$

Plotting eq 6 gave curve a in graph 6. For the racemate, $Y_{(R\text{-}3+S\text{-}3)} = Y_{RS\text{-}3} = 0.33$; this 67/33 *RS*-**2**/*RS*-**3** ratio is the biggest effect that can be attained in this extreme second-order model, which substantiates the intuition that the effect is much too big for a second-order scheme (section 3).

The fourth-order model fits the three independent sets of experimental data, which strongly suggests that it is correct. It suggests in turn that all of the rate-determining processes are fourth order with respect to the substrate and that the corresponding rate constants all similar or identical.

7. Kinetics

What we have done are competition experiments: competitions between the single, "racemic", heterochiral process and the two enantiomeric pairs of homochiral processes. We therefore know the *relative* overall rate constants—they are about the same—but not the *absolute* ones. This approach was tried because it is a great deal simpler than one that will in principle provide the absolute rate constants along with a rate law and because we suspected that the rate constants are the same (section 6).

We must have a sequence of steps of which the rate-determining (slowest) step somehow involves four substrate-derived units. There is very little information in the literature on these steps and in particular on their absolute kinetics and for good reason: all of the steps are very rapid, and the system is experimentally difficult. One can identify at least the first two steps: these must be (1) reaction between the camphors and an e^-_{am} and then (2) pairing of the resulting free ketyls with potassium ion. Dewald has specialized in this field, and Song and he have recently published the first thorough investigation of the kinetics of the reaction of a ketone with the e^-_{am} and sodium ion at −34 °C by the stopped-flow technique.[31] They chose 2,2,4,4-tetramethylpentan-3-one as the substrate and deduced a rate law for the disappearance of the e^-_{am} that is second order with respect to the e^-_{am} and first order with respect to ketone and sodium ion. With this ketone, the phenomenon we see is constitutionally blocked and a reaction with the ammonia occurs instead. As in our case, a late step in a sequence of steps is rate determining so that the kinetics of the early steps that correspond to ours, in particular the first two, are not available. Song and Dewald proposed a mechanism that we think is unlikely, but the finding that a late step is rate determining is the essential point.

Prior to this, two groups had studied the kinetics of the reaction of e^-_{am} with acetone by pulse radiolysis at 22–23 °C under pressure in the absence of alkali metal ions.[32] Both assumed that the first step is rate determining and deduced second-order rate constants of about the same magnitude for it: 1.7×10^8 and 9.0×10^7 L mol^{-1} s^{-1}. However, it could well be that a later step is rate determining here as well,[33] and this would explain why these rate constants suggest that the first step is *not* diffusion controlled as one would expect. In any event, these rate constants are probably different when alkali metal ions are present. This is all of the basic kinetic information that is available.

Our hypothesis was that our processes are ketyl disproportionations. A great deal is known about the absolute kinetics of radical disproportionations, because these and combinations are the two fundamental radical self-reactions.[16,34] As introduced under section 3, it is well-established that these are all near diffusion controlled or diffusion controlled.

8. Stereochemistry of Radical Disproportionations, Evidence that an α-Hydrogen Is Transferred in Our Processes, and Partial Stereochemistry of These Transfers

In contrast, relatively little is known about the stereochemistry of radical disproportionations,[35] and in no instance have the homo- and heterochiral disproportionations of a chiral radical—the bona fide disproportionation counterparts of our processes—been investigated.

Beckwith and Easton[35b] have shown that the best geometry for the transfer of the β-hydrogen atom from a radical in a radical disproportionation is when the β-carbon–hydrogen bond and the semioccupied p orbital are coplanar. The reason for this is that transfer is favored by overlap between the fragmenting bond and the p orbital. A chiral radical must be used to obtain this stereochemical information, and a racemic mixture was generated in cyclohexane solution from a racemic precursor, but dissection into the homochiral and heterochiral disproportionations was not envisaged. The radical chosen was (2*RS*,6*RS*)-4-(*tert*-butyl)-2,6-dimethylcyclohexyl and the pseudoaxial β-hydrogens are transferred about 8 times more rapidly than the pseudoequatorial ones.

We wanted the same dissection for our processes and to thereby learn more about them. Note that the Beckwith–Easton experiment shows which hydrogens are transferred preferentially, but not to where, whereas ours show where the hydrogens go, but not which, the *exo*- or the *endo*-hydrogen or both, are transferred. Note also that if planar ketyls are involved, the angles between the semioccupied p orbital and the fragmenting carbon–*exo*- and –*endo*-hydrogen bonds are very similar in our case; i.e., the hydrogens are almost equivalent.

The experiments that had led to our disproportionation hypothesis had been done inter alia[5b] with the labeled camphor *R*-**1**-*3,3-d*$_2$.[5c] One of the deuteriums was transferred, but we did not know which and also not what happens in the case of the racemate *RS*-**1**-*3,3-d*$_2$. (This was just before we realized that *R*-**1** and *RS*-**1** behave differently.) To answer these questions, Huffman and Wallace[10b] later carried out experiments with the complete set of singly α-labeled camphors: *exo*-*R*-**1**-*3-d*, *endo*-*R*-**1**-*3-d*, *exo*-*RS*-**1**-*3-d*, and *endo*-*RS*-**1**-*3-d*. Using almost the same procedure[36] as in the present experiments and our earlier ones with *R*-**1**-*3,3-d*$_2$ and *R*-**1**, they found the following: (1) essentially only *exo*-deuteriums are transferred; (2) the extent of deuterium transfer into the isoborneols **3** is the same for *exo*-*R*-**1**-*3-d* and *exo*-*RS*-**1**-*3-d*; and (3) the extent of deuterium transfer

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[31] Song, W. M.; Dewald, R. R. *J. Chem. Soc., Perkin Trans. 2* **1989**, 269–273.

[32] (a) Perkey, L. M.; Farhataziz. *Int. J. Radiat. Phys. Chem.* **1975**, *7*, 719–730. (b) Schindewolf, U.; Wünschel, P. *Can. J. Chem.* **1977**, *55*, 2159–2164.

[33] In the discussion in ref 32a, it was suggested that protonation could be the rate-determining step.

[34] (a) Pryor, W. A. *Free Radicals*; McGraw-Hill: New York, 1966; Chapter 20. (b) Ingold, K. U. In *Free Radicals*; Kochi, J. K., Ed.; Wiley: New York, 1973; Vol. I, Chapter 2. (c) Gibian, M. J.; Corley, R. C. *Chem. Rev.* **1973**, *73*, 441–464. (d) Nonhebel, D. C.; Walton, J. C. *Free Radical Chemistry*; Cambridge University Press: Cambridge, U.K., 1974; Chapter 8. (e) Dannenberg, J. J.; Baer, B. *J. Am. Chem. Soc.* **1987**, *109*, 292–293.

[35] (a) Agosta, W. C.; Wolff, S. *J. Am. Chem. Soc.* **1976**, *98*, 4316–4317; **1977**, *99*, 3355–3361. (b) Beckwith, A. L. J.; Easton, C. *J. Am. Chem. Soc.* **1978**, *100*, 2913–2914. Agosta and Wolff had found the same effect as Beckwith and Easton, but in an intramolecular case and it was much stronger. The intramolecularity is undoubtedly the reason the effect is stronger than in Beckwith's case, which is intermolecular. For the disproportionation of the C_9–C_{12} cycloalkyl radicals to give (*Z*)- and (*E*)-cycloalkenes, see: (d) Wojnarovits, L. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1449–1451.

[36] The only difference is that they worked at −70 °C and we at about −77 °C. The overall borneol/isoborneol ratios were about 40/60 for both *exo*-*R*-**1**-*3-d* and *endo*-*R*-**1**-*3-d* (50/50 for *R*-**1** at about −77 °C) and about 86/14 for both *exo*-*RS*-**1**-*3-d* and *endo*-*RS*-**1**-*3-d* (90/10 for *RS*-**1** at about −77 °C).

into the borneols **2** is greater from *exo-RS*-**1**-*3-d* than from *exo-R*-**1**-*3-d*.

Although *exo-R*-**1**-*3-d* and *exo-RS*-**1**-*3-d* lost some of the label by exchange, one can extrapolate to the unlabeled system as follows: (1) both the homo- and the heterochiral transfers involve essentially only the *exo*-hydrogens; (2) the isoborneols **3** are mainly formed via a homochiral transfer of a hydrogen from the exo to the endo position (exo → endo transfer); and (3) the borneols **2** are formed via both homochiral and heterochiral transfers from the exo to the exo positions (exo → exo transfers).

9. Mechanism

We return to the conclusion that we have a sequence of steps and that the rate-determining step involves four substrate-derived units. The only reasonable interpretation is that we have in fact a bimolecular rate-determining step, but one that involves either (a) a substrate-derived trimer and a monomer or (b) two substrate-derived dimers. The dimers or trimers (and the tetramers) must be made up from charged species—because only charges and cations will hold them together—and are best considered ketyl dimers and trimers,[5e] and the monomer in (a) could be a ketyl monomer or in principle the substrate itself. Path a involving ketyl trimer and monomer and path b could first lead to a ketyl tetramer[37,38] or directly to products. If the transfer indeed occurs between ketyls or between ketyl and substrate, then hydrogen atoms are probably transferred: these are then typical radical reactions, i.e., hydrogen atom abstractions. The simplest such mechanism is via path b, i.e., mutual abstractions, disproportionations, but Huffman and Wallace have recently uncovered the first evidence that lithium ketyls (whose degree of association is unknown) derived from *R*-**1** (and *RS*-**1**) actually do react with *R*-**1** (and *RS*-**1**).[10b] *We cannot distinguish between these options*, which are not even exhaustive.

We have nevertheless tried hard to translate the simplest path, path b,[37] into a complete kinetic scheme, i.e., to link it to the fourth-order model derived in the curve fittings, but are not sure whether the scheme we have developed is entirely consistent. In its simplest version, it involves *statistical* distributions via sequences that are entirely diffusion controlled.[39] One confusing complication is that if these steps are rapid enough—they do *not* have to be diffusion controlled—and provided the rate constants are different, mixing effects come into play. Mixing control will then compensate for the difference in the rate constants, which would *appear to be* the same.[40] For all of these reasons and because this or any other model is still very speculative, the scheme will only be developed to the extent that it illustrates certain key points below and gives a feeling for the chemistry that must be involved.

In general, the fourth-order model can be immediately linked with the known propensity of ketyls to associate, and this correlation is certainly valid. (The first mechanism that comes to mind is that disproportionations occur within ketyl tetramers, but this can probably be excluded.) It is known from ESR studies that alkali metal ketyls derived from saturated ketones rapidly associate.[5a,41] This is specific information on ketyls, but it is also known that alkali metal ketyls, alcoholates,[42] and enolates[43] *all* associate to give the same kinds of structures that are determined by the Coulombic attraction between the metal ions and the negatively charged oxygens: they all contain metal ion–oxygen cores to which the organic parts are appended. There is now a wealth of information on the *self-organization* and reactivity of enolates, in particular crystal structures that are not available for ketyls, and it is well-established that their reactions are dictated by this self-organization.[43] We think that, essentially, our findings mean that this is also true for ketyls.

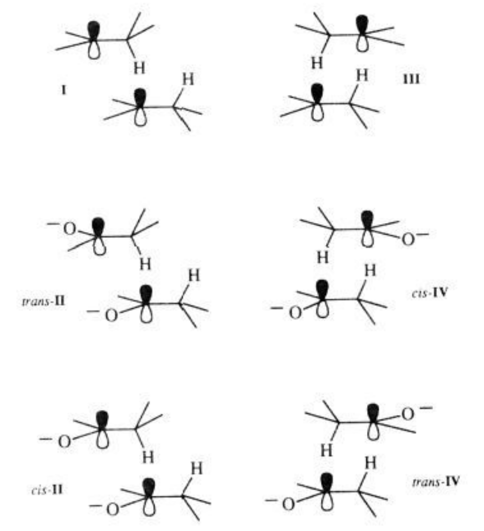
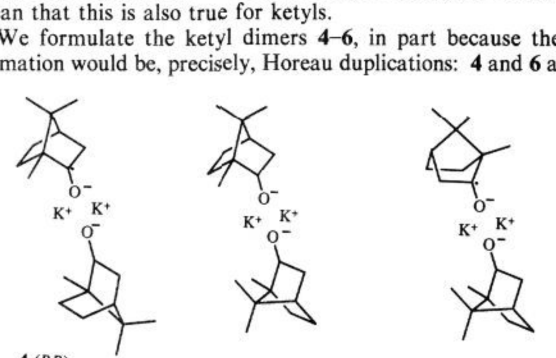


Figure 7. Topologies I–*trans*-IV.

We formulate the ketyl dimers **4**–**6**, in part because their formation would be, precisely, Horeau duplications: **4** and **6** are homochiral dimers, and **5** is a heterochiral dimer. The depicted structures are supported by the ESR data, and there are also well-characterized dimeric enolates that have similar structures.



4 (*RR*) **5** (*RS*) **6** (*SS*)

We had thought[5b–e] that *second-order* disproportionations à la Horeau (section 6) occurred within these dimers and now conclude that these are blocked if the dimers are involved, which can now be rationalized. In the dimers, the ketyl units would be far away from each other. To disproportionate, they would have to fold toward each other, but it would still be difficult for either β-hydrogen in one unit to come into contact with the radical carbon atom in the other, and the massive lipophobic solvation spheres around the large, bridging potassium ions may prevent this folding.

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(37) The tetramers being built up from dimers seems the simplest pathway: Heinzer, J.; Oth, J. F. M.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1848–1862.

(38) Direct alkylation of mainly one lithium enolate tetramer formed from (*RS*)-norbornenone is implied by the formation of mainly one trimer with one unit alkylated: (a) Horner, J. H.; Vera, M.; Grutzner, J. B. *J. Org. Chem.* **1986**, *51*, 4212–4220. See also: (b) Paquette, L. A.; Moorhoff, C. M.; Maynard, G. D.; Hickey, E. R.; Rogers, R. D. *J. Org. Chem.* **1991**, *56*, 2449–2455. Reference 38a depicts two structures for the alkylated trimer, RRR′ and RSR′, but it is clear that RRR′ was drawn by mistake and RSR′ deduced by NMR techniques. Reference 38b quotes the RRR′ structure and this led to Professor Grutzner realizing that the correct structure, as determined later by X-ray analysis, is actually RRS′.

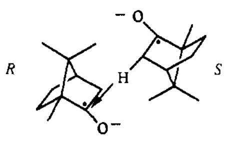
(39) Cf. Fischer's collision model for the self-reactions of *tert*-butyl: Schuh, H. H.; Fischer, H. *Helv. Chim. Acta* **1978**, *61*, 2463–2481.

(40) See refs 5d and 10b and: Baldyga, J.; Bourne, J. R. *Chem. Eng. Sci.* **1990**, *45*, 907–916, and references cited therein. Bourne, J. R.; Ravindranath, K.; Thoma, S. *J. Org. Chem.* **1988**, *53*, 5166–5168. Rys, P. *Acc. Chem. Res.* **1976**, *9*, 345–351. Francis, A. W. *J. Am. Chem. Soc.* **1926**, *48*, 655–672. See also: Meijs, G. F.; Bunnett, J. F.; Beckwith, A. L. J. *J. Am. Chem. Soc.* **1986**, *108*, 4899–4904. Tremelling, M. J.; Bunnett, J. F. *J. Am. Chem. Soc.* **1980**, *102*, 7375–7377.

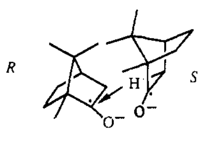
(41) Mao, S. W.; Nakamura, K.; Hirota, N. *J. Am. Chem. Soc.* **1974**, *96*, 5341–5349, and references cited therein.

(42) (a) Weiss, E.; Alsdorf, H.; Kühr, H.; Grützmacher, H. F. *Chem. Ber.* **1968**, *101*, 3777–3786. (b) Bradley, D. C.; Mehrotra, R. C.; Gaur, D. P. *Metal Alkoxides*; Academic Press: London, 1978.

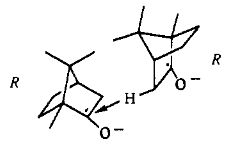
(43) Jackman, L. M.; Lange, B. C. *Tetrahedron* **1977**, *33*, 2737–2769. Seebach, D. *Proc. Robert A. Welch Found. Conf. Chem. Res.* **1984**, *27*, 93–145. Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624–1654. Williard, P. G.; McEwan, G. J. *J. Am. Chem. Soc.* **1989**, *111*, 7671–7672. Williard, P. G.; Hintze, M. J. *J. Am. Chem. Soc.* **1990**, *112*, 8602–8604. Maetzke, T.; Hidber, C. P.; Seebach, D. *J. Am. Chem. Soc.* **1990**, *112*, 8248–8250. Maetzke, T.; Seebach, D. *Organometallics* **1990**, *9*, 3032–3037.



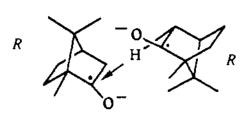
7: *trans*-**IV**, heterochiral, *S exo→R exo*



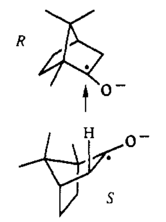
11: *cis*-**II**, heterochiral, *S exo→R exo*



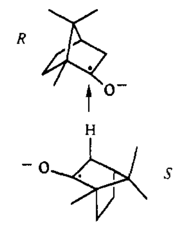
8: *cis*-**IV**, homochiral, *R exo→R exo*



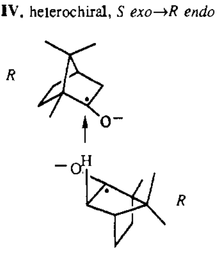
12: *trans*-**II**, homochiral, *R exo→R exo*



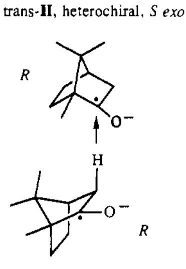
9: *cis*-**IV**, heterochiral, *S exo→R endo*



13: trans-**II**, heterochiral, *S exo→R endo*



10: *trans*-**IV**, homochiral, *R exo→R endo*



14: *cis*-**II**, homochiral, *R exo→R endo*

Figure 8. Topologies **7–14**.

Two dimers then reacting with each other via path b would amount to a second Horeau duplication. Overall, this would amount to a tetramerization, and this also holds for path a, i.e., first a trimerization and then a reaction with a fourth unit. We go on and conclude that regardless of the exact nature of the transfer and pathway, we have effectively *a double Horeau duplication.*

10. Further Stereochemistry

The transition states of the disproportionation of simple radicals such as ethyl or *tert*-butyl have been pictured as head-to-tail arrangements,[34,44,45] while those of more complex radicals, in particular chiral ones, have not been discussed so far. This kind of arrangement is depicted as I, with parallel carbon–carbon bonds and Beckwith's geometry in the upper radical and the same conformer for the lower radical (to which the hydrogen is transferred). I is not a transition state but serves to define the topology of one of two stereochemically distinct transition states.

In the case of ketyls, I corresponds to two diastereoisomers with the charged oxygens on the same side, either *cis*, *cis*-II, or *trans*, *trans*-II, to each other (Figure 7). Rotation of either unit in I, *cis*-II, and *trans*-II around a vertical axis passing roughly through the trajectory of the hydrogen atom that is transferred leads to two continua. One is symbolized by I, *cis*-II, and *trans*-II and the other by III, *cis*-IV, and *trans*-IV, in which the carbon–carbon bonds are again parallel (180° rotation) but the oxygens at opposite ends. The latter continuum has not been considered so far, presumably for steric reasons.

We know (section 8) that our transfers are exo → exo and exo → endo transfers. Transposing this information into camphor-derived ketyls and these into *cis*- and *trans*-II and *cis*- and *trans*-IV first defines all such possible transfers. Ketyls are formulated,[46] but the topologies are the same for other mechanistic variants. There are four transfers for each topology: **7–10** for IV and **11–14** for II. The information that there is a single heterochiral exo → exo transfer pinponts **7** and **11**, of which **7** seems much more favorable. There seems to be single favorable topology in each four: for IV, this is **7**, and for II, this is **12**, which symbolizes a homochiral exo → exo transfer. This suggests that **7** with the topology IV is involved and that the two homochiral transfers, exo → exo and exo → endo, therefore also involve topology IV, thus **8** and **10**. To verify these tentative conclusions, we plan to explore the continua **7–14** by molecular mechanics calculations.

These conclusions fit the scheme in which the dimers **4–6** disproportionate with each other. Because the dimers have the potassium–oxygen–potassium–oxygen squares between the ketyl units, the oxygens are at opposite ends as in IV if a unit in one dimer reacts with a unit in another: **7**, **8**, and **10** would characterize the reacting units of the dimers.

Can one further define the actual transition states for the disproportionations that may correspond to the topologies **7**, **8**, and **10**? First, the C(2)–C(3) bonds would certainly not be parallel as depicted. If the ketyl units are planar as assumed so far (**4–14**), then the semioccupied p orbitals and the fissioning carbon–*exo*-hydrogen bonds are not coplanar: locally, the *exo*- and *endo*-hydrogens are almost equivalent. However, second, it could be that the ketyls are not planar. This is suggested by the fact that ketyl radicals—which would result if the ketyls were protonated on oxygen—for example, 1-hydroxycyclohexyl[47a,c]—are definitely pyramidal, and by the assignment of a pyramidal structure with the hydroxy group bent in the endo direction precisely to camphor ketyl radical.[47b] If our camphor ketyls had the same kind of geometry,[48] then the carbon–exo-hydrogen bonds would be more coplanar with the radical orbital and would therefore be transferred preferentially, as observed. Third, one can guess that the semioccupied orbital to which the hydrogen atom is transferred and the carbon–hydrogen bond from which that hydrogen comes would be about collinear, and fourth, one can estimate the distance between the reacting units from Benson's contact model[16d] (van der Waals contact).

11. Homooligomerizing Scalemic Monomers

We have also indirectly reexemplified that statistical oligomerization or condensation of scalemic monomers leads to homochiral oligomers with strongly amplified ec's. This is a simple and powerful principle that has been experimentally realized in isolated cases for dimerization up to pentamerization.[25,28,29b,49] The relation between the amplification and the degree of oligomerization is given by progressively more extreme S curves,[29] the first and third of which are those in graph 4. Amplification decreases with increasing degree of homooligomerization, and the higher the degree, the less is it likely—the more mixed oligomers there are and the more of them are formed. This balance makes small homochiral oligomers the most interesting. A case in question

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[44] The terms head-to-head and head-to-tail come from the early, disproven hypothesis that disproportionation involves abstraction of an α-hydrogen atom at the radical carbon atom in a head-to-head arrangement, followed by migration of a β-hydrogen.[34]

[45] See, for example, Benson's contact transition state[16d] and Dannenberg and Baer's orbital correlation arguments.[34e]

[46] For clarity, only one of the enantiomeric heterochiral transfers is shown in each case, for example, the downward one in the case of **7** (the upward one would symbolize the enantiomeric transfer), and also only one of the enantiomeric homochiral transfers.

[47] (a) Micheau, J. C.; Despax, B.; Paillous, N.; Lattes, A.; Castellano, A.; Catteau, J. P.; Lablache-Combier, A. *Nouv. J. Chim.* **1981**, *5*, 257–260, and references cited therein. Lloyd, R. V.; Causey, J. G. *J. Chem. Soc., Perkin Trans. 2* **1981**, 1143–1147. Alipour, E.; Micheau, J. C.; Paillous, N. *Recl. Trav. Chim. Pays-Bas* **1988**, *107*, 503–506. (b) Gloux, J.; Guglielmi, M.; Lemaire, H. *Mol. Phys.* **1970**, *19*, 833–852. Review: (c) ref 14b.

[48] Enolatizations—the abstraction of protons from ketones by bases—and radical disproportionations, the mutual abstraction of hydrogen atoms, show the same stereoelectronic effect for the same reason, maximum overlap. In particular, exo deprotonation in our very substrate is very well-documented (review: Toullec, J. *Adv. Phys. Org. Chem.* **1982**, *18*, 1–77). These effects and our near-exclusive exo-hydrogen transfers can be correlated.[10b]

[49] Okada, M.; Sumitomo, H.; Atsumi, M. *J. Am. Chem. Soc.* **1984**, *106*, 2101–2104.

would be the formation of small homopeptides from amino acids.[25,28d]

12. Experimental Section

Gas Chromatography (GC). The analyses without enantioseparation were performed on a Hewlett-Packard 5880 A instrument fitted with a flame ionization detector (FID) and a 30 m × 0.25 mm fused silica Supelcowax capillary column (Supelco), the enantioseparations in 1989 on a Carlo Erba 4160 instrument fitted with a FID and a 15 m × 0.27 mm glass capillary column coated at Firmenich with 10% nickel bis[(1*R*)-(3-heptafluorobutyryl)-camphorate] (Fluka) in OV 101[18c] and combined with a Shimadzu Chromatopac C-R3A integrator, and the enantioseparations in 1991 on the same instrument fitted with a commercial (Macherey-Nagel) 45 m × 0.25 mm fused silica column coated with octakis(3-*O*-butyryl-2,6-di-*O*-pentyl)-γ-cyclodextrin and the same integrator. The carrier gas was He throughout. Analyses without enantioseparation: about two analyses per run, means in Table I; analytical errors for $Y_{(R\text{-}3+S\text{-}3)}$ $\leq\pm$ about 0.001 (0–1.000 scale).[21a] Enantioseparations in 1989 (borneols **2** and isoborneols **3**): samples dissolved in hexane; $\bar{v}$ = 40 cm/s; temperature program 100 °C isothermal for 40 min, then 1 °C/min to 140 °C; typical retention times, *R*-**3** 20.2 min, *S*-**3** 21.9 min, *R*-**2** 25.7 min, *S*-**2** 27.3 min, unseparated *R*-**1**, *S*-**1** 60 min; two to four analyses per run, means in Table I; analytical errors for the ec's Y' ± about 0.02–0.03 (0–1.00 scale).[21b] Enantioseparations in 1991 (camphors **1**): samples dissolved in pentane; $\bar{v}$ = 30 cm/s; temperature program 80 °C isothermal for 2 min, then 1 °C/min to 140 °C; typical retention times *R*-**1** 17.4 min, *S*-**1** 18.6 min; three analyses per sample, analytical errors for the ec's X $\leq\pm$ about 0.001 (0–1.000 scale).[21c] The small-scale preparative GLC in the low-conversion runs was carried out on a Carlo Erba Fractovap GT instrument fitted with a thermal conductivity detector and regular Carbowax-packed glass columns.

Substrates. We used the same *R*-**1** [Siegfried purum purchased in 1971(?)] and *RS*-**1** (Lotti, Genève, purchased in 1975) as before[5c,d] and *S*-**1** that was a gift from W. Oppolzer and had been made from *S*-**2** (Aldrich) according to the procedure of Stevens and co-workers.[50] For the low-conversion runs, *R*-**1** and *RS*-**1** were purified by standard flash chromatography[51] followed by Kugelrohr distillation. Before this purification, *R*-**1** and *RS*-**1** contained traces of impurities: both contained the corresponding alcohols, *R*-**1** two further, unidentified compounds, and *RS*-**1** a single further, different, unidentified compound. Flash chromatography removed all three impurities from *R*-**1** (the gas chromatogram showed a single, huge peak) and the two alcohols from *RS*-**1** (one huge and one minute peak). *S*-**1** also gave a single, huge peak. These chemical purities were established by GC without enantioseparation under the conditions used in the analyses in graph 1, at the sensitivity used in the low-conversion experiments. The ec's measured on the cyclodextrin column were 99.6% for *R*-**1**, 98.3% for *S*-**1**, and 50.1% for *RS*-**1**.[21c] The $[\alpha]_D$'s of the purified samples were measured again[5c,d] on a Perkin-Elmer 241 polarimeter (ethanol solution): *R*-**1** had $[\alpha]^{25}_D$ +44.7° (*c* 10.01), *RS*-**1** $[\alpha]^{25}_D$ 0.00° (*c* 10.02), and *S*-**1** $[\alpha]^{25}_D$ −43.7° (*c* 10.00). The ec's determined by GC and the $[\alpha]_D$'s were consistent, extrapolation to ec's of 100% giving $[\alpha]^{25}_D$ +45.1° and −45.2°.

We used the same potassium as before (Fluka, 98%, 0.4% Ca, Na).[5b-d] For the high-conversion runs, THF (Baker) was purified by passing it through basic Al_2O_3, and for the low-conversion runs, it was then purified further by refluxing over and distilling from $LiAlH_4$.

Table I

	run[a]	$X_{R\text{-}1}$	$Y_{(R\text{-}3+S\text{-}3)}$	$Y'_{R\text{-}2}$	$Y_{R\text{-}3}$
1	run 19, m, lc	0.00400	0.496	0.00	0.00
2	run 1, m	0.00400	0.429	0.00	0.00
3	run 2, m	0.00400	0.510		
4	run 3, m	0.00400	0.410		
5	run 15, m	0.00400	0.406		
6	run 16, m	0.00400	0.460		
7	ref 5c, m	0.00400	0.460		
8	ref 5c, m	0.00400	0.480		
9	run 23	0.0170	0.370	0.00	0.00
10	run 13, m	0.106	0.329	0.170	0.00
11	run 6, m	0.107	0.425	0.190	0.00
12	run 22, m, lc	0.153	0.367	0.250	0.00
13	run 5, m	0.183	0.306	0.270	0.00
14	run 14	0.194	0.272	0.240	0.0200
15	run 9, m	0.211	0.287	0.300	0.00
16	run 4, m	0.235	0.233	0.310	0.00
17	run 10, m	0.250	0.250	0.320	0.00
18	run 11	0.262	0.242	0.310	0.0300
19	run 7, m	0.328	0.201	0.410	0.00
20	run 21, m, lc	0.400	0.135	0.471	0.143
21	run 8, m	0.406	0.139	0.460	0.180
22	run 12	0.420	0.129	0.410	0.210
23	run 24, m	0.449	0.111	0.520	0.280
24	run 25, m, mc	0.449	0.107	0.510	0.285
25	run 17	0.500	0.0970		0.495
26	run 17, m	0.500	0.0970		0.505
27	run 18	0.500	0.119	0.480	0.480
28	run 18, m	0.500	0.119	0.520	0.520
29	run 26	0.500	0.102		
30	run 20, lc	0.500	0.101	0.485	0.500
31	run 20, m, lc	0.500	0.101	0.515	0.500
32	run 24	0.551	0.111	0.480	0.720
33	run 25, mc	0.551	0.107	0.490	0.715
34	run 12, m	0.580	0.129	0.590	0.790
35	run 8	0.594	0.139	0.540	0.820
36	run 21, lc	0.600	0.135	0.529	0.857
37	run 7	0.672	0.201	0.590	1.00
38	run 11, m	0.738	0.242	0.690	0.970
39	run 10	0.750	0.250	0.680	1.00
40	run 4	0.765	0.233	0.690	1.00
41	run 9	0.789	0.287	0.700	1.00
42	run 14, mc	0.806	0.272	0.760	0.980
43	run 5	0.817	0.306	0.730	1.00
44	run 22, lc	0.847	0.367	0.750	1.00
45	run 6	0.893	0.425	0.810	1.00
46	run 13	0.894	0.329	0.830	1.00
47	run 23, m	0.983	0.370	1.00	1.00
48	run 1	0.996	0.429	1.00	1.00
49	run 2	0.996	0.510		
50	run 3	0.996	0.410		
51	run 15	0.996	0.406		
52	run 16	0.996	0.460		
53	ref 5c	0.996	0.460		
54	ref 5c	0.996	0.480		
55	run 19, m, lc	0.996	0.496	1.00	1.00

[a] Abbreviations: m, mirrored; lc, low conversion; mc, medium conversion (0.17 equiv of potassium).

High-Conversion Procedure.[5c] About 14 mL of NH_3 (Multigas, 99.9%) was distilled under Ar through a short piece of plastic tubing from the storage cylinder into a hand-graduated Schlenk tube[52] maintained in a CO_2/acetone bath.[13] While stirring with a Teflon-coated magnetic stirring bar under Ar,[12] a solution in 2.4 mL of THF of a total of 60–65 mg (about 0.4 mmol) of *R*-**1** or *S*-**1** or *RS*-**1** or a weighed-in mixture of *R*-**1** and *S*-**1** or *R*-**1** and *RS*-**1** was pipetted in at once (Ar flush), the temperature stabilized, and then a single 13–17-mg piece of K (0.33–0.44 mmol) added. The piece was cut under mineral oil in the air from a bigger chunk to approximately the desired weight with a knife. The clean and shiny piece was rinsed in hexane and quickly dried on tissue paper (pincers) in the air, weighed in oil, again rinsed and quickly dried, and—no longer shiny—quickly dropped (pincers) into the liquid ammonia–THF solution (Ar flush). The piece dissolved/reacted in/with the stirred solution within about 1 min, leaving a characteristic blue trail in the solution, which was weakly cloudy-white at the end, when excess solid NH_4Cl was added. The cooling bath was removed and the NH_3 evaporated through a Vigreux column fitted with a drying tube filled with KOH pellets. The residue was taken up in H_2O and extracted with Et_2O. The combined extracts were dried over $MgSO_4$,

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filtered, and the Et_2O distilled off through a 21 × 1 cm spiral column. The residue was directly analyzed by GC. Example (run 11): 15.4 mg of *R*-**1** (ec 99.6%, 15.3 mg of *R*-**1**, 0.1 of mg *S*-**1**), 46.0 mg of *S*-**1** (ec 98.3%, 45.2 mg of *S*-**1**, 0.8 mg of *S*-**1**), totalling 16.1 mg of *R*-**1** + 45.3 mg of *S*-**1** = 61.4 mg (0.40 mmol), ec 26.2% (Table I; $X_{R\text{-}1} = 0.262$), 14.8 mg of K (0.38 mmol, 0.95 equiv), which dissolved within 49 s. After workup, the crude mixture was analyzed once on the Supelcowax column, (*R*-**1** + *S*-**1**) = 61.48%, (*R*-**2** + *S*-**2**) = 29.21%, (*R*-**3** + *S*-**3**) = 9.31%, conversion about 77% [100 − (61.48 − (29.21 + 9.31)) = 77.04], (*R*-**2** + *S*-**2**)/(*R*-**3** + *S*-**3**) = 75.8/24.2 (Table I; $Y_{(R\text{-}3+S\text{-}3)} =$ 0.242), and once on the nickel heptafluorobutyrylcamphorate column, *R*-**2**/*S*-**2** = 31/69 (Table I; $Y'_{R\text{-}2} = 0.310$), *R*-**3**/*S*-**3** = 3/97 (Table I; $Y'_{R\text{-}3} = 0.030$).

The low-conversion procedure was essentially the same, except that somewhat less K was used and the volumes and amounts of substrate were correspondingly much larger. Example (run 21): A solution of 800.6 mg of *RS*-**1** (400.3 mg of *R*-**1**, 400.3 mg of *S*-**1**) and 200.9 mg of *R*-**1** (ec 99.6%, 200.1 mg of *R*-**1**, 0.8 mg of *S*-**1**), totalling 600.4 mg of *R*-**1** + 401.1 mg of *S*-**1** = 1001.5 mg (6.6 mmol), ec 60.0% (Table I; $X_{R\text{-}1} = 0.600$), in 39 mL of THF was syringed via septum into 230 mL of NH_3 in a three-necked flask maintained in a CO_2/acetone bath under Ar. To the resulting, stirred (Teflon-coated magnetic stirring bar) solution was added 2.3 mg of K (0.06 mmol, 0.009 equiv), which dissolved within 15 s. After workup, the crude mixture was analyzed three times on the Supelcowax column, (*R*-**1** + *S*-**1**) = 99.587, 99.585, 99.591%, mean 99.588%, (*R*-**2** + *S*-**2**) = 0.353, 0.358, 0.356%, mean 0.356%, (*R*-**3** + *S*-**3**) = 0.057, 0.057, 0.053%, mean 0.056%, conversion about 0.8%, (*R*-**2** + *S*-**2**)/(*R*-**3** + *S*-**3**) = 86.1/13.9, 86.3/13.7, 87.0/13.0, mean 86.4/13.6 (Table I; $Y_{(R\text{-}3+S\text{-}3)} = 0.136$). Part of the (*R*-**1** + *S*-**1**) was removed by small-scale preparative GC, and two ~1-mg samples were collected in glass capillaries. Each was dissolved in hexane and each analyzed once on the Supelcowax column. Sample I: (*R*-**1** + *S*-**1**) = 77.68%, (*R*-**2** + *S*-**2**) = 19.04%, (*R*-**3** + *S*-**3**) = 3.28%, (*R*-**2** + *S*-**2**)/(*R*-**3** + *S*-**3**) = 85.3/14.7. Sample II: (*R*-**1** + *S*-**1**) = 83.19%, (*R*-**2** + *S*-**2**) = 14.39%, (*R*-**3** + *S*-**3**) = 2.42%, (*R*-**2** + *S*-**2**)/(*R*-**3** + *S*-**3**) = 85.6/14.4. Sample I was analyzed four times on the nickel heptafluorobutyrylcamphorate column, *R*-**2**/*S*-**2** = 52/48, 52/48, 53.5/46.5 (no integration in one analysis), *R*-**3**/*S*-**3** = 86/14, 84/16, 85/15, 87.5/12.5, and sample II once, *R*-**2**/*S*-**2** = 54/46, *R*-**3**/*S*-**3** = 86/14, mean *R*-**2**/*S*-**2** = 52.9/47.1 (Table I; $Y'_{R\text{-}2} =$ 0.529), mean *R*-**3**/*S*-**3** = 85.7/14.3 (Table I; $Y'_{R\text{-}3} = 0.857$).

The runs and the results of the gas chromatographic analyses [except the proportions of (*R*-**1** + *S*-**1**) on the Supelcowax column] are listed in Table I.

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Chemistry of Oxaziridines. 17.[1] *N*-(Phenylsulfonyl)(3,3-dichlorocamphoryl)oxaziridine: A Highly Efficient Reagent for the Asymmetric Oxidation of Sulfides to Sulfoxides

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Abstract: The synthesis, structure, and enantioselective oxidations of a new chiral *N*-sulfonyloxaziridine **12c** [3,3-dichloro-1,7,7-trimethyl-2′-(phenylsulfonyl)spiro[bicyclo[2.2.1]heptane-2,3′-oxaziridine]] are reported. This oxidant, which exhibits remarkably high and predictable ee's for the enantioselective oxidation of prochiral sulfides to sulfoxides, is prepared in three steps from (+)- or (−)-camphor in 50% overall yield. Steric effects are primarily responsible for the molecular recognition and are predictable using a simple active-site model where the nonbonded interactions between the R_L and R_S groups of the sulfide (R_L–S–R_S) and the active-site surface are minimized in a planar transition-state structure. The fact that alkyl aryl sulfides give high ee's in nonpolar solvents suggests that there is also a stereoelectronic component to the molecular recognition. High ee's (>90%) are anticipated for those sulfides where the difference in size of the groups directly bonded to the sulfur atom is large, i.e., aryl, *tert*-butyl vs CH_2R (R = H, alkyl, benzyl, etc). The X-ray structure and studies with the dihydro, difluoro, and dibromo oxaziridines **12a**, **12b**, and **12d** reveal that the exceptional enantioselectivities displayed by **12c** are a consequence of a molecular cleft or groove, defined by the oxaziridine chlorine atoms and phenylsulfonyl group, on the active-site surface.

Enantiomerically pure sulfoxides are widely used intermediates for the synthesis of optically active materials.[2] The reaction of an organometallic reagent with a diastereomerically pure menthyl *p*-toluenesulfinate, the Andersen procedure, is the method most often employed for the synthesis of chiral nonracemic sulfoxides.[3,4] However, this procedure is limited in the synthesis of highly functionalized sulfoxides and for certain dialkyl sulfoxides.[5] The asymmetric oxidation of a prochiral sulfide with an enantiopure oxidizing reagent, at least in principle, is an attractive alternative because (i) the sulfoxide would be available in one step and (ii) those sulfoxides not readily accessible by the Andersen procedure could be realized.

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