

RACEMIZATION AND RESOLUTION IN THE ORGANIC SOLID STATE

by

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ABSTRACT

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Two examples of the simplest type of organic solid-state reaction - the thermal interconversion of optical isomers - have been extensively studied by means of polarimetry, differential scanning calorimetry, and X-ray powder diffraction.

The first reaction investigated was the reverse Diels-Alder reaction and recombination of the cyclopentadiene-fumaric acid adduct. Polycrystalline samples of (+)-enantiomer (m.p. 176°) racemize completely in the solid state from 130° to 165°. First-order kinetics ($\Delta H^\ddagger = 40.0 \text{ kcal mole}^{-1}$, $\Delta S^\ddagger = 14 \text{ cal deg}^{-1} \text{ mole}^{-1}$) are strictly obeyed; the racemization rate is insensitive to variations in crystal size and optical purity. The reaction, which is only five times slower than the melt rate extrapolated to these temperatures (for the melt from 176° to 194°, $\Delta H^\ddagger = 29.7 \text{ kcal mole}^{-1}$, $\Delta S^\ddagger = -6.9 \text{ cal deg}^{-1} \text{ mole}^{-1}$) occurs throughout the polycrystalline sample rather than at crystallite boundaries, dislocations, or other preferred sites. Phase studies show that the product separates as a racemic compound (m.p. 186°) which forms a eutectic (at 165°) with the resolved enantiomers. From 165° to 176°, the racemization shows autoacceleration and sigmoid-shaped kinetic curves characteristic of concurrent reactions in the solid and melt phases.

The second system studied was that formed between R-(-)- and S-(+)-1,1'-binaphthyl, and surprisingly, resolution, rather than racemization, was observed to occur from 76° to 158°. This unprecedented solid-state resolution is made possible by a solid-solid phase change from a racemic compound

(m.p. 145°) to a eutectic mixture (m.p. 158°) of crystals of pure enantiomers, at temperatures where interconversion occurs in the reactant-product interface. Polycrystalline 1,1'-binaphthyl samples of very low optical activity having the correct phase content (racemate plus crystals of only one enantiomer) for a controlled resolution can be easily and reproducibly prepared. These samples resolve from $[\alpha]_D = 2^\circ$ to $[\alpha]_D = \underline{ca.} 210^\circ$ (in either (+) or (-) directions) in less than one hour at 150°. The limit of resolution ($[\alpha]_D = \pm 245^\circ$) is attained simply by recrystallization of the resolved sample from acetone. The resolution therefore involves the conversion of all of a racemic material to only one enantiomer. Kinetic studies of the solid-state resolution show a smooth development of optical activity with time. A Prout-Tompkins analysis indicates that crystallites of growing enantiomer spread throughout the racemic sample, requiring 62 kcal mole⁻¹ activation energy.

Crystallization of completely racemic 1,1'-binaphthyl melt in a closed system gives rise to optical activity. The probability distribution of 200 individual crystallizations is symmetric about $[\alpha]_D = 0^\circ$ and proves that optically active samples can be created under absolutely spontaneous conditions (i.e., in the complete absence of external dissymmetric influences).

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1 INTRODUCTION

Modern knowledge of the organic solid state largely consists of information on the structure and physical properties of a great variety of materials. Not nearly so well-developed, however, is our understanding of chemical reactivity in organic solids. Usually, systems which are chemically unstable have been avoided. For example, many of the techniques used for the physical investigations of organic solids - from ultraviolet spectroscopy to semiconductor physics - require stable crystals of high purity. Any chemical reaction complicates the investigation, causing measured properties to change with time, and eventually causing the breakdown of carefully grown single crystals.

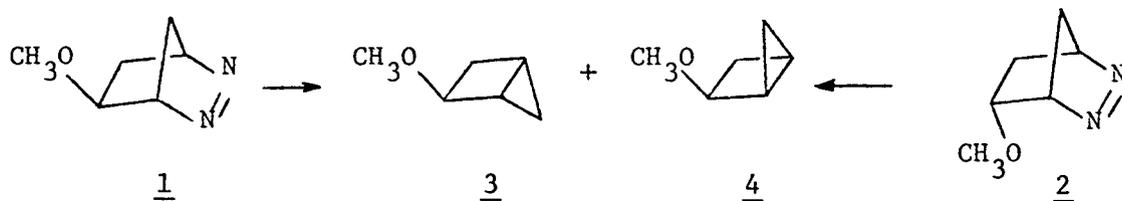
Even in organic chemistry, where solid reagents are encountered daily, the solution phase has been the medium preferred for investigations. Here, the view is generally held that reactions in organic solids are too sluggish to be of synthetic utility, or too complex to be amenable to common physical organic analysis.

There are, however, some well-established areas of endeavour where the reactivity of the organic solid state has been of great interest. The decomposition of solid organic compounds, especially those related to organic explosives, have until fairly recently accounted for most of the research with reacting organic solids.¹ In several reviews from

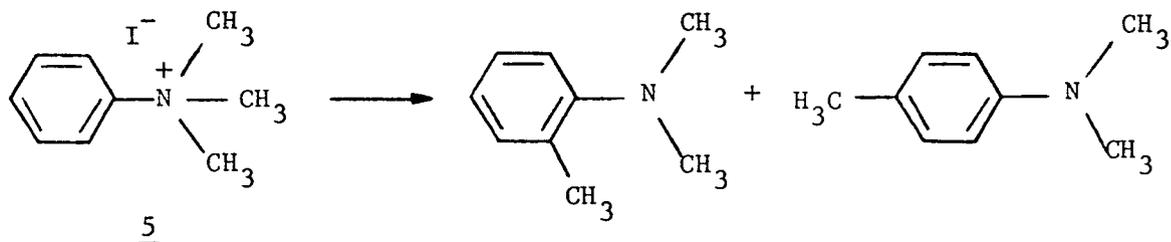
1963-1966, Morawetz² considered the reported examples of reactions in organic solids, and drew attention to the surge of interest in solid-state polymerizations, now being widely explored.

One fascinating aspect of reactions in organic solids, which has received the attention of several groups, is the possibility of stereochemical control by the crystal lattice. The very elegant and detailed investigations of Schmidt and Cohen^{3,4} into the photodimerizations of crystalline monomers are well known. These workers demonstrated how the geometrical orientation and spacing of reacting molecules in the lattice determines product stereochemistry. Such "topochemical control" explains the observed products in most photoreactions of organic solids. More recent investigations⁵ have shown that even some of the exceptions may still be subject to controls, but of a different nature. A case in point is 9-cyanoanthracene,⁵ which exists in a "head-to-head" arrangement in the crystal lattice, but gives a "head-to-tail" photodimer. This apparent failure of lattice control was understood with the discovery of suitable dislocations in the crystal across which there are "head-to-tail" pairs of molecules. Reaction across the dislocation then forms the observed stereoisomer. This result underscores the influence of crystalline order, both in the regular lattice and at some dislocations, on the course of solid-state reactions.

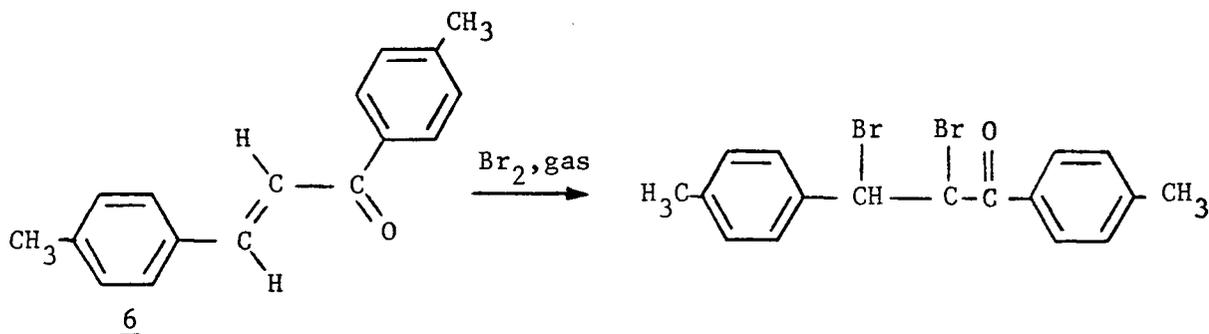
Other accounts of the control exercised by the solid state on product distribution and stereochemistry have been given. Some recent reports demonstrate the wide variety of organic reactions which are susceptible to solid-state perturbation. Allred and Smith⁶ have examined the thermal decomposition of the hetero-substituted norbornene epimers 1 and 2:



Thermalolysis of the exo epimer 1 in the gas phase or photolysis in solution gave the bicyclopentanes 3 and 4, with the trans isomer 3 in slight excess; however, photolysis of crystalline 1 produced almost totally the cis isomer 4. Analogous reactions of the endo epimer 2 showed preferential formation of 4 in fluid media but an excess of 3 in the crystalline state. This reversal of stereospecificity was explained by formation of a short-lived diradical which was inverted in fluid media but retained its conformation in the restricted environment of the solid state. Likewise, Site,⁷ in a study of the decomposition of the quaternary ammonium salt 5 in the melted and solid states, noticed that



reaction in the solid gives a higher proportion of ortho-substitution than reaction in the melt. A striking illustration of crystal lattice control has been given by Penzien and Schmidt,⁸ who investigated the reaction of bromine vapor with single crystals of 4,4'-dimethylchalcone (6), an achiral compound which crystallizes in an enantiomorphic space group. The resulting dibromide was obtained with one enantiomer in



excess. Hence, this process constitutes an absolute asymmetric synthesis. When the reaction is performed in solution, no activity develops. Another gas-solid reaction, the air oxidation of some steroids, was reported by Brenner *et al.*⁹ Reaction occurred on heating or on irradiation, but depended strongly on the polymorphic form of each compound. Some steroids were very susceptible to oxidation in one crystal modification, and totally unreactive in another.

Solid-state controls have been demonstrated with free radicals generated either thermally^{10,11} or under ionizing radiation² in organic materials. Evidence of the expected greater cage effect has been presented both in the form of increased ratios of recombination reactions to hydrogen abstraction outside the cage,¹⁰ and as increased stereoselectivity¹¹ in an organic glass over that in solution. In free radical addition polymerizations in the solid state, which have recently

been reviewed,¹² the polymer often bears some orientational ("topotactic") relationship to the monomer lattice.^{2c,2d} In fact, the very prospect of producing polymer chains which are more regularly oriented than those produced in solution has been a major reason for the renewed interest in reactions in organic solids.

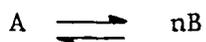
From reviewing the reported examples of organic solid-state reactivity, it seems that most are either chance observations or else detailed examinations of systems which tend to be rather complex. If a good understanding of the mechanisms of reactions in organic solids is to be achieved, then the very simplest of reactions should be investigated. These should provide insight into the most elementary processes occurring in the reacting organic solid. In this thesis the "simple reaction" will be regarded as a thermal (organic) solid-state reaction which always consists of two components. The types of reactions this definition includes and excludes can be considered as follows.

First of all, the organic solid-state reactions which either proceed under irradiation or are radiation-induced and then proceed thermally are relatively complex processes. In the case of ultraviolet radiation, the electronic energy levels of the molecular solid must be taken into account, as well as the mechanism of energy transfer within the solid. Relevant to this is the discussion by Sarti-Fantoni^{13,14} in connection with the photochemical reactions of 9-substituted anthracenes. If ionizing radiation is used, rather indiscriminant bond breaking may result, and there can be considerable damage to the crystal structure.²

The definition also restricts the possible systems to those of

two components. This limitation follows from the fact that systems of three or more components can possess exceedingly complex phase relationships. The task of identifying the reactive phases could become very difficult in such systems. Therefore, reactions of a simple compound to give at least two different products (such as thermal decompositions) are excluded, as are reactions of two (or more) different molecules to give one or several products. In the latter case, if the two reactants are in separate phases (two solids, solid and liquid, etc.), any mechanistic description must also include the process of diffusion in solids if reaction is to proceed beyond a monolayer of product molecules at the interface between the reactants.

The "simple reactions" are therefore those which have only a single reactant and a single product. The reactant must be either neat or contain only the product as an impurity. Reactions performed in inert solid media (e.g. glass, host crystal or polymer matrix) are not "simple" because the inert medium constitutes a third component. The "simple reaction" can therefore be represented as:

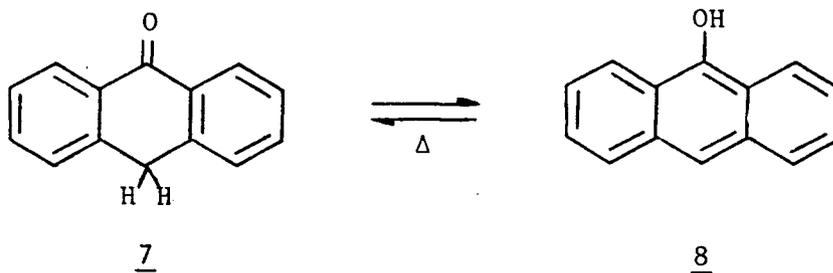


where n is a small integer. When n equals one, the solid reaction is an isomerization. When n is two, the reaction is a thermal monomer-dimer conversion. One illustration of this is the dimerization of aryl isocyanates in the solid state.¹⁵ The reverse process, the simple decomposition of a dimer into its monomer fragments, is exemplified by the thermal reaction of 9-cyanoanthracene¹⁴ dimer. Processes where

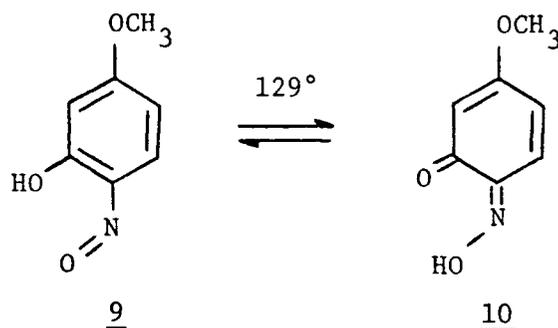
n is three or greater are found in the formation of oligomers, but the restrictions of "simplicity" makes examples rare. That is, if a monomer \rightarrow trimer reaction proceeds via a dimer with a discrete existence, the total system becomes one of three components.

Examples of thermal solid-state isomerizations are somewhat more common than those of thermal monomer-dimer reactions. Some of the reported examples are in need of more experimental work, but a few have been investigated in considerable detail.

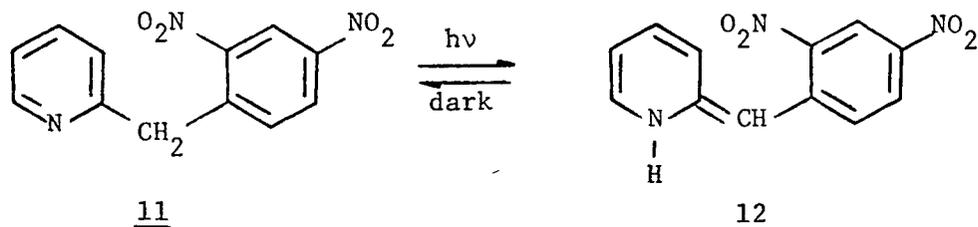
There are a few illustrations of thermal solid-state tautomerism. Pope and coworkers¹⁶ observed that anthrone (7) readily tautomerizes to anthranol (8) in the solid-state from 84° to 158°. In fact, anthranol is easily prepared by heating anthrone at its melting point



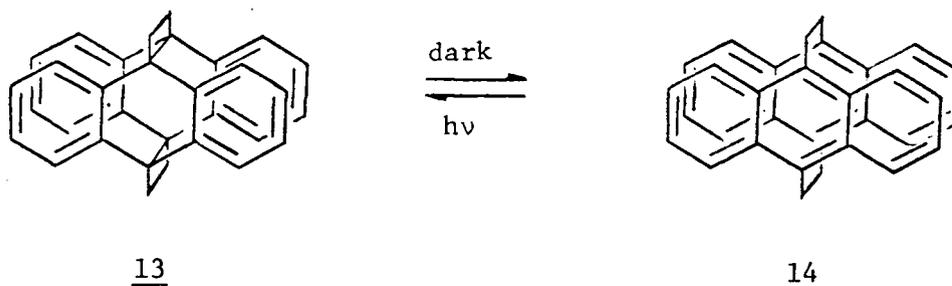
then quenching quickly to room temperature. No kinetics were run, but the half-life at room temperature in benzene solution is about 2 hours. The nitrosophenol 9, which crystallizes from benzene in a "green form", undergoes a solid-state conversion at 129° to a "red form" (m.p. 154°) which has been shown by crystallographic studies¹⁷ to have the *o*-quinone monoxime structure 10. The same tautomerism exists in solution, and both forms have intramolecular hydrogen bonding. If the pale yellow



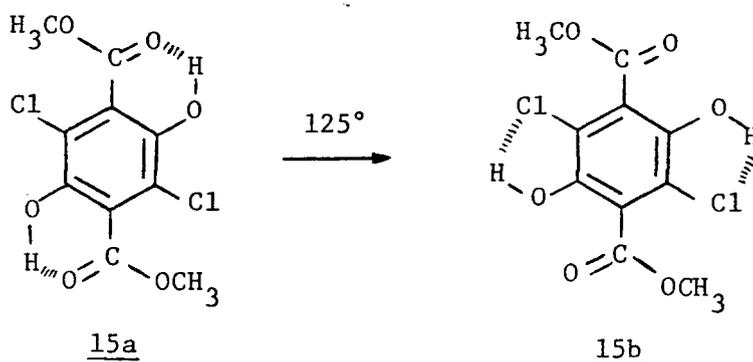
crystals of the dinitrobenzylpyridine 11 are irradiated with light of wavelength 4000 Å, deep blue crystals are produced. When the photo-product is kept in the dark, thermal reconversion to 11 occurs in a few



hours. A crystal structure determination of 11 led Seff and Trueblood¹⁸ to suggest tautomerism (via the oxygen of the *o*-nitro group) between structures 11 and 12. Another thermal-photochemical interconversion in the solid state was revealed by a crystallographic study¹⁹ of the photoisomer (structure 13) of bi(anthracene-9,10-dimethylene) (14). The photoisomer 13, which could be produced by solid-state irradiation of 14 or simply by crystallization from chloroform in the light, undergoes a dark reconversion to its valence tautomer 14 in the solid state.



An interesting case of stereoisomerism at an oxygen-carbon bond due to hydrogen bonding in the solid state was published recently by Curtin and Byrn.²⁰ The compound dimethyl-3,6-dichloro-2,5-dihydroxyterephthalate exists in both a yellow form (m.p. 140°) and a white form (m.p. ca. 185°). Studies with deuterated phenolic groups, and infrared and nuclear quadrupole resonance investigations are consistent with structure 15a and 15b, representing the yellow and white forms,



respectively. A thermal solid-state conversion from the yellow to the white form occurs at 125°.

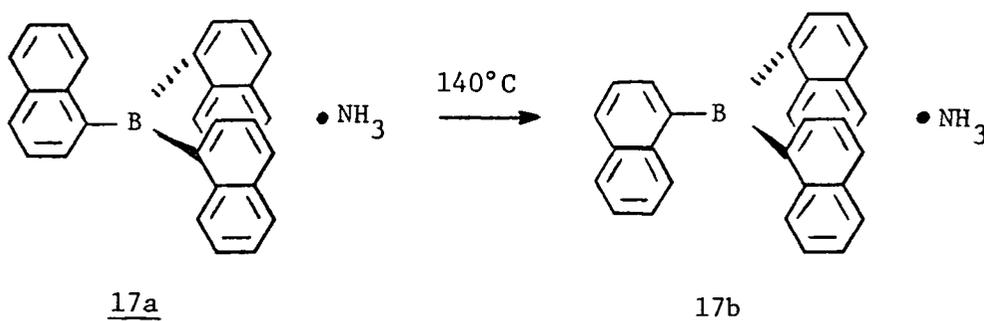
A kinetic study of the isomerization of solid cis-azobenzene (16) has been performed by Tsuda and Kuratani.²¹ The cis-trans conversion

was investigated in samples which were powdered and compressed in KBr



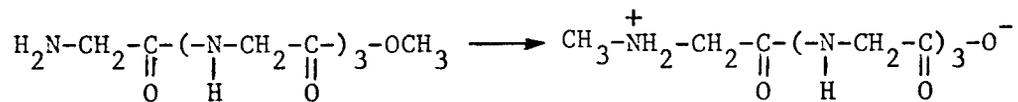
discs. The reaction occurs in the solid state, giving rise to sigmoid-shaped kinetic curves, which were sensitive to the method of sample preparation, and the extent of grinding.

One case of a solid-state reaction between conformational isomers has been reported. Several years ago Brown and Sujishi²² observed what they postulated as the conversion on heating of an unsymmetrical isomer 17a to a symmetrical isomer 17b of a tri- α -naphthyl borine-ammonia adduct. The solid-state conversion was discovered by noting that the



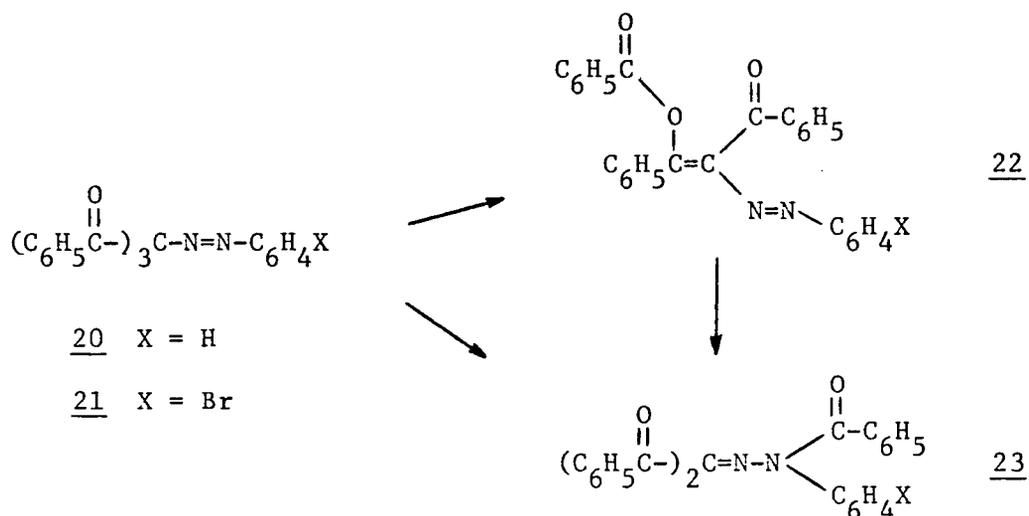
pressure of dissociated ammonia was quite different for each material, and that the highly dissociated adduct converted to the more stable adduct on heating to 140°.

Some illustrations of thermal isomerization via group migrations in the solid state exist. Almost twenty years ago, Sluyterman and coworkers²³ examined the thermal reactions of tetraglycine methyl ester (18) in the solid state. Heating neat 18 at 100° produced sarcosyl



triglycine (19), the result of a methyl migration, which is perhaps most feasibly explained by an intermolecular shift from the ester end of one molecule to the amino end of a neighbour. At higher temperatures (185°) and in solution at 100° polycondensation is the main reaction. A kinetic run at 100° showed S-shaped character; the induction period was shortened somewhat by grinding the sample.

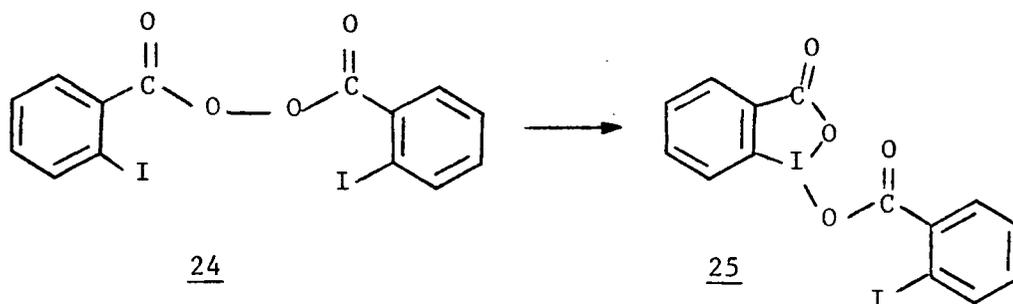
Another rearrangement in the solid state has been studied in detail by Curtin and collaborators.^{24,25} Two different arylazotribenzoylmethanes, 20 and 21, undergo migration of a benzoyl group both to oxygen (forming the enol benzoate 22) and to nitrogen (forming the hydrazone 23). The



study was backed by an X-ray crystal structure analysis of the bromo-derivative 21, by differential thermal analysis, and by observation of

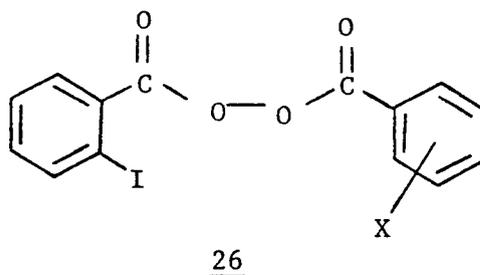
the reaction both in single crystals on a microscope hot stage and in a polycrystalline sample by powder diffractometry. For example, when 20 is heated at 5°/min, melting occurs at ca. 124°, and is followed immediately by rearrangement to an equimolar mixture of 22 and 23, accompanied by the evolution of heat. Further heating converts the isomer 22 to 23 over a temperature range of 40°, and finally the pure hydrazone melts at 200°. Examination of mixtures of the three compounds 20, 22 and 23 suggested a eutectic temperature above 110°. The reaction proceeds in the solid state in the temperature range 70-105°. Although the system is vastly simpler than most decompositions, it unfortunately involves three components, and a more detailed description of phase reactivities and relationships would be rather difficult.

An initial report by Leffler²⁶ of the solid-state isomerization of 2,2'-diiododibenzoyl peroxide (24) has received further attention



from a crystallographic standpoint by Gougoutas.²⁷ The reaction occurs in several weeks in the crystalline state at room temperature, and overnight at 110°. The product benziodoxole 25 produced in single crystals of 24 is remarkably well-ordered and bears a topotactic relationship to the reactant lattice. This geometrical correspondence

suggests that half of the phenyl rings flip through 180° during reaction, a molecular movement which is surprisingly large in terms of the spacing allowed in the lattice. A study of the related peroxides 26, where X = hydrogen, 2-bromo, 2-chloro, 2-fluoro, 3-chloro and 4-nitro showed



that all react in the solid state,^{27b} and some²⁸ undergo single crystal-single crystal topotactic transformations similar to the diiodo compound 24.

Some simple isomerizations, which occur easily on melting,²⁹⁻³³ may also proceed in the solid state. Reinvestigation of reactions in these systems below the melting points concerned may reveal some unusual solid-state behaviour.

Interest in chemical reactions in organic solids began in this laboratory with the work of Pincock and Kiovsky^{34,35} on reactions in frozen solutions. It was discovered that common chemical reactions occurring in organic and aqueous solvents showed surprising features below the freezing point of the solvent. A detailed kinetic study proved that these observed changes in kinetic order and large rate accelerations could be completely accounted for simply by the increased concentration of reactants in liquid regions of the frozen solvent. It was unnecessary to invoke any novel solid-state effects. These

liquid regions necessarily exist above the eutectic temperature of the solvent-solute phase system. It was therefore emphasized that in all rate studies in frozen systems, even those as far as 70° below the melting points concerned, any reaction in a liquid phase must be quantitatively separated out before valid conclusions regarding solid-state phenomena can be drawn.

A logical extension of the ideas developed during the work on reactions in frozen, inert solvents was to consider from a kinetic standpoint thermal reaction in a neat solid reactant. In general the product will lower the melting point of the reactant, and reaction can potentially occur in both the solid and the liquid phases at temperatures above the eutectic of the system. If the system is "simple", i.e., has only two components, the important phase relationships may be easy to establish.

For this reason, the first system studied was the thermal mutarotation of polycrystalline α -D-glucose.³⁴⁻³⁶ Isothermal kinetic runs below the melting point of pure α -D-glucose (146°) possessed an S-shaped character. Reaction began slowly in the initially solid sample, but as the product β -D-glucose developed, the reaction accelerated and the sample began to melt; maximum rate was observed on complete melting, whereafter the rate decreased as equilibrium was approached. The sigmoid nature of the kinetic curves could be explained by neglecting any reaction in the solid phase, and considering only that in the developing liquid phase. The reaction accelerates because the reacting liquid phase increases in volume at the expense of the unreactive solid phase.

A second study,³⁷ that of the thermal isomerization of polycrystalline endo- and exo-5-norbornene-2,3-dicarboxylic anhydrides (27 and 28,

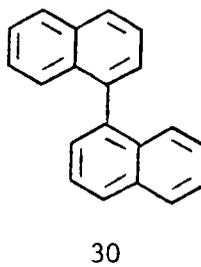
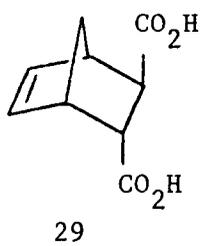
respectively) above and below their melting points, demonstrated the



type of kinetics which can arise from reaction occurring simultaneously in both solid and liquid phases. Chemical equilibrium in the two-component systems occurs at an equimolar mixture of isomers, and can be approached from either side. Solid endo isomer, heated at 120-164°, eventually melted, but unlike α -D-glucose, the form of the kinetic curves was not sigmoid, but first order. That is, reaction occurred as if the system were totally melted, even though the solid phase was present. Phase studies showed that solid endo isomer was a "crystalline liquid"³⁷ above 94°, and that molecules in this phase possessed mobility and could isomerize equally as fast as those in the liquid phase. Solid exo anhydride could not isomerize as readily as the endo adduct, and this fact was reflected in the shape of the kinetic curves. Rate equations for both reactions were developed by assuming that the reaction in the solid phase is first order. The rate equation could be integrated, and by assigning different values to the solid-state rate constant, the form of both the endo and exo kinetic curves could be generated. A separation of the kinetic contributions of both solid and melt phase reactions was therefore accomplished.

In view of the facility with which reaction proceeds in solid endo

and exo anhydrides, we decided to examine the possibility of solid-state racemization in two optically active systems. The first, also a Diels-Alder adduct, was (+)-bicyclo[2.2.1]hept-5-ene-trans-2,3-dicarboxylic acid (29). The second was a simple hydrocarbon, (+)-1,1'-binaphthyl (30). Since the two components in each of these systems are

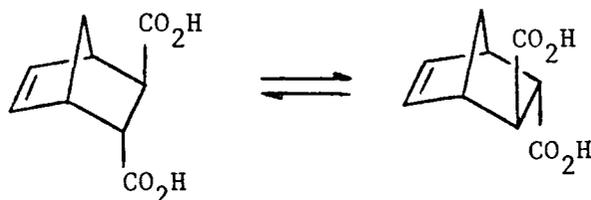


enantiomers, the phase relationships are simplified. Any true solid-state reaction, if it occurs at all, should be easily recognized and, hopefully, examined more closely.

The results of our study of the cyclopentadiene-fumaric acid adduct (29) are presented in Section 2 of the thesis. Our investigations (and unexpected findings!) with the 1,1'-binaphthyl system are reported in Section 3.

2 RACEMIZATION OF (+)-BICYCLO[2.2.1]HEPT-5-ENE-TRANS-2,3-DICARBOXYLIC
ACID (29) IN THE LIQUID AND SOLID STATES³⁸

This molecule, which owes its dissymmetry to two chiral carbon atoms, can conceivably interconvert with its enantiomer in the melt and in solution, and possibly also in the solid state.



29, (+)-enantiomer (m.p. 176°), (±)-racemate (m.p. 186°)

The racemic compound 29 was prepared^a from the addends (cyclopentadiene and fumaric acid) using the method of Koch.³⁹ Resolution to the (+)-enantiomer was effected via the brucine salt,⁴⁰ using multiple recrystallizations from acetone-water. The purified (+)-diacid 29, was more highly resolved (different preparations gave specific rotations of $[\alpha]_D^{26} = +137^\circ$ and $+147^\circ$ in acetone) and possessed a higher melting point (177-179°) than that originally reported⁴⁰ ($[\alpha]_D^{20} = +89^\circ$, m.p. 166-168°). Although the optical purity of the resolved diacid remains unknown, the kinetic results presented below

^a The preparation and the resolution of (+)-diacid 29 was performed in this laboratory by M.M. Tong, before the work reported in this thesis was begun.

did not depend, even in the solid state, on the extent of resolution.

2.1 Racemization in the Liquid State

2.1.1 The Melt Phase

Kinetic runs in the melt phase were performed from 176 - 194°. The method involved heating individual sealed ampules containing purified (+)-29 in a constant temperature bath. Racemization to $[\alpha]_D = 0^\circ$ occurred, and although there was a slight yellowing of samples, this was not significant before the material was essentially racemic. Product studies showed that at long reaction times (greater than 15 half-lives), some polymerization occurred, but the initial reaction was simply an interconversion of enantiomers.

When the results were plotted as first-order reactions ($\log[\alpha]/[\alpha]_0$ vs. time)^b, straight lines were obtained to over 90% reaction (Figure 1). The observed first-order rate constants are listed in Table I. Half-lives for racemization varied from 3 min at 194° to 12 min at 176°. The ease of reaction at the melting point of (+)-29 suggests that any solid-state reaction, even if slower by one or two orders of magnitude, might still be measurable.

2.1.2 The Solution Phase

The racemization of (+)-29 was also studied in tetralin solution, at temperatures where the pure diacid 29 would be solid (131-152°). Again, first-order plots were straight lines, and the observed rate constants are shown in Table I.

^b All of our specific rotations $[\alpha]$ were measured at the sodium D line. The subscript D will hereafter be omitted for simplicity.

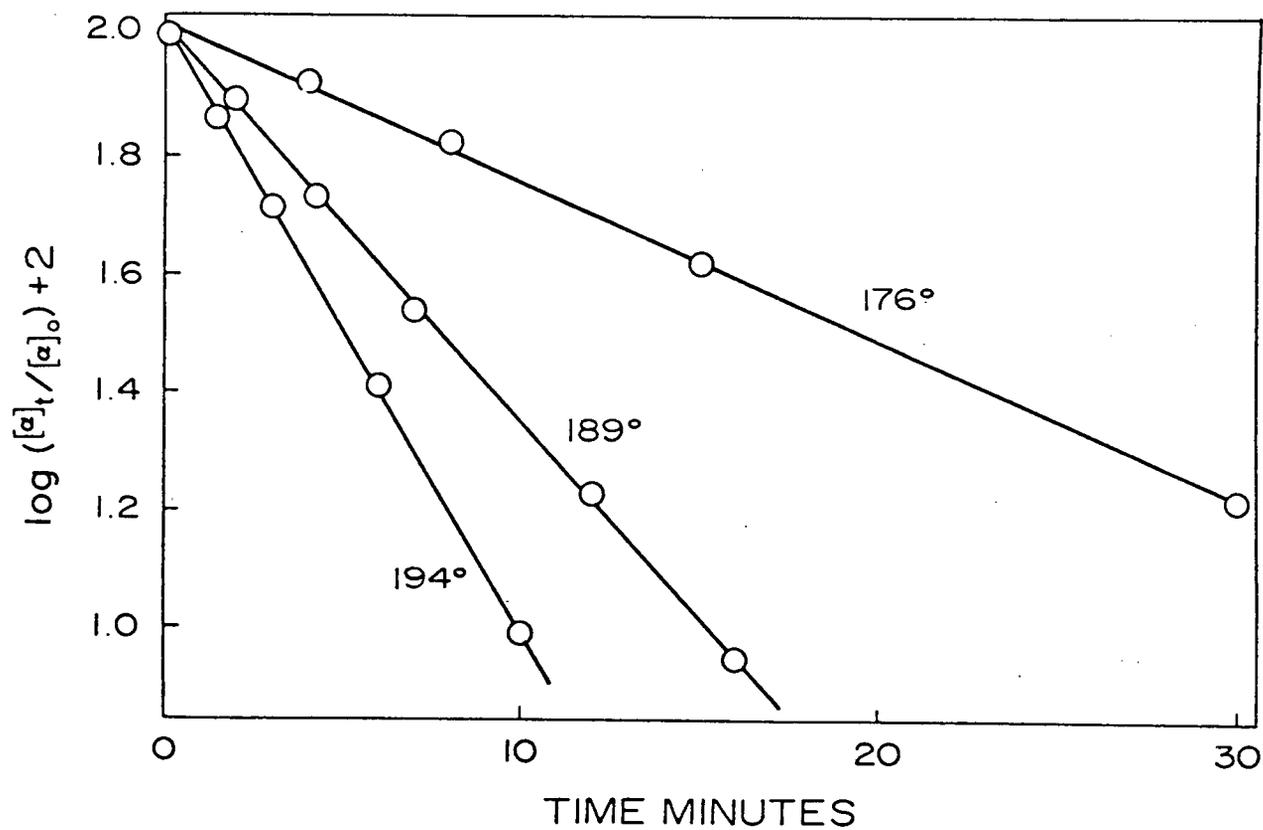


Figure 1. First-order kinetic plots for racemization of neat (+)-diacid 29 in the melt phase.

Table I
 First-Order Rate Constants for Racemization of (+)-29 in Solid, Melt
 and Solution

Temperature, °C	$k_{\text{obs}} \times 10^5, \text{sec}^{-1}$	Phase
194.3	380	melt
189.1	248	"
181.8	147	"
176.6	103	"
166.2	8.3 ^a	melt + solid
161.2	7.09 ^a	" "
155.4	4.23	solid
152.4	2.76	"
140.2	0.654	"
130.9	0.227	"
152.4	6.98	solution
143.7	2.93	"
131.3	0.834	"

^a Initial rate constant.

The activation parameters for racemization in the melt and in solution were obtained from a plot of $\log k_{\text{obs}}/T$ vs. $1/T$ as required by the Eyring equation:

$$[1] \quad \log \frac{k_{\text{obs}}}{T} = \log \frac{\kappa}{h} + \frac{\Delta S^\ddagger}{2.303R} - \frac{\Delta H^\ddagger}{2.303RT}$$

where κ and h are Boltzmann's and Planck's constants, respectively, T is the absolute temperature, and ΔS^\ddagger and ΔH^\ddagger are the entropy and enthalpy of activation. The free energy of activation, ΔG^\ddagger , is obtained from the relation:

$$[2] \quad \Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$$

and the temperature chosen for comparison of the reaction in different phases was 150° . The results are listed in Table II and plotted in Figure 2. The rate in tetralin solution is seen to be some 2.0-2.5 times

Table II

Activation Parameters for Racemization of (+)-29 in Solid, Melt, and Solution

	k_{obs} (150°), sec^{-1}	ΔG^\ddagger (150°), kcal mole^{-1}	ΔH^\ddagger kcal mole^{-1}	ΔS^\ddagger $\text{cal mole}^{-1}\text{deg}^{-1}$
melt	11.3×10^{-5} ^a	32.6	29.7	-6.9
solid	2.05×10^{-5}	34.0	40.0	+14
solution	5.14×10^{-5}	33.2	33.6	+0.8

^a Extrapolated from the temperature range 176 - 194° .

slower than that in the melt (extrapolated). This small difference is reflected in a marginally higher free energy of activation in tetralin solution. Such a small solvent effect is typical of reverse Diels-Alder

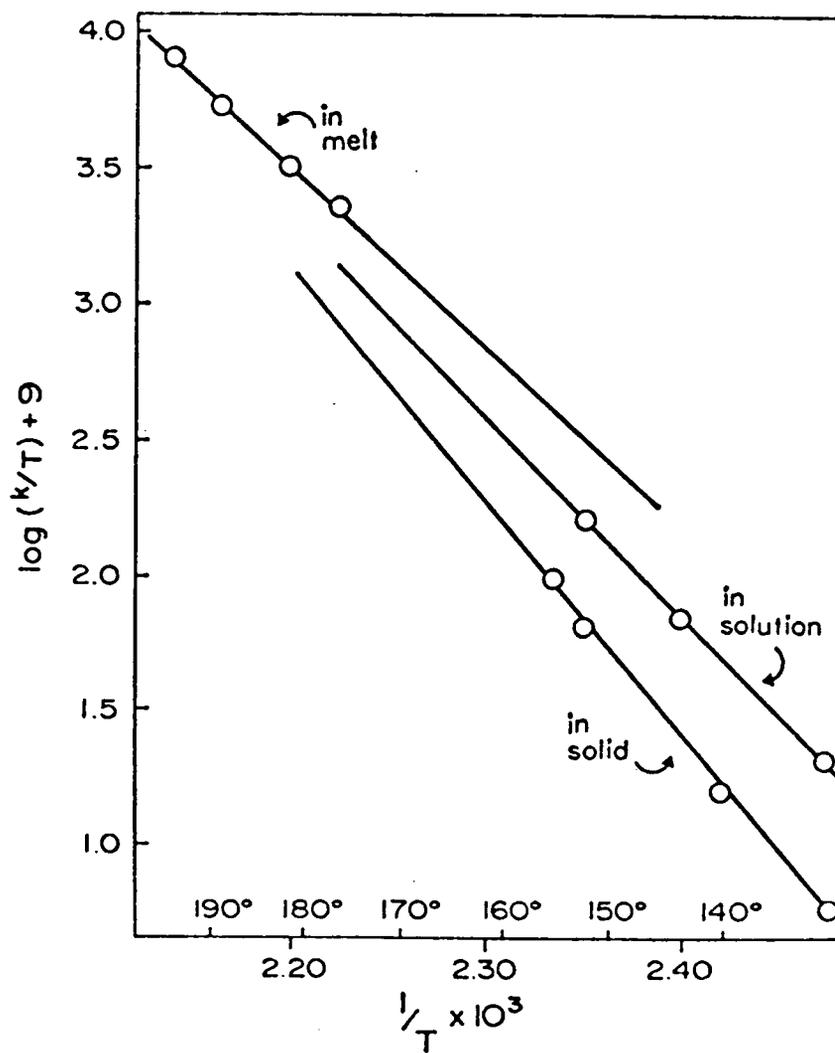


Figure 2. Relation of $\log(k_{obs}/T)$ to reciprocal temperature for racemization of (+)-enantiomer 29 in melt, solid, and solution (in tetralin) phases.

reactions and recombinations.⁴¹ Also, the magnitude of the absolute rate constants in both liquid media is close to that of similar reverse Diels-Alder reactions.^{42,43}

2.2 Racemization in the Solid State

The racemization of the (+)-diacid 29 was explored below its melting point (176°). Polycrystalline samples of resolved 29 were sealed in ampules and held at various temperatures below 176°. It was found that racemization could indeed occur as low as 130°. Moreover, the kinetic form of the reaction from 130° to 155° was first-order. Plots of $\log[\alpha]/[\alpha]_0$ vs. time were again linear to at least 90% racemization (see Figures 3 and 4). There were no inhibition periods as have been virtually always observed for solid-state organic¹ and inorganic^{44a} decompositions. The kinetic results were insensitive to grinding, different batch preparations or sample history. Also absent was any dependence on the extent of resolution of the samples.

The kinetic simplicity of the reaction from 130° to 155° permitted treatment of the observed rate constants (Table I) in the same manner as those for reaction in the melt and in solution. The plot of $\log k_{\text{obs}}/T$ against reciprocal temperature is shown in Figure 2. Activation parameters (Table II) were obtained from the resulting straight line. The rate constant at 150° is seen to be only about 5 times smaller than that obtained from the melt extrapolated to 150°.

In the temperature range 161° to 166°, a departure from simple first-order kinetics was observed (Figures 4 and 5). A sigmoid shape

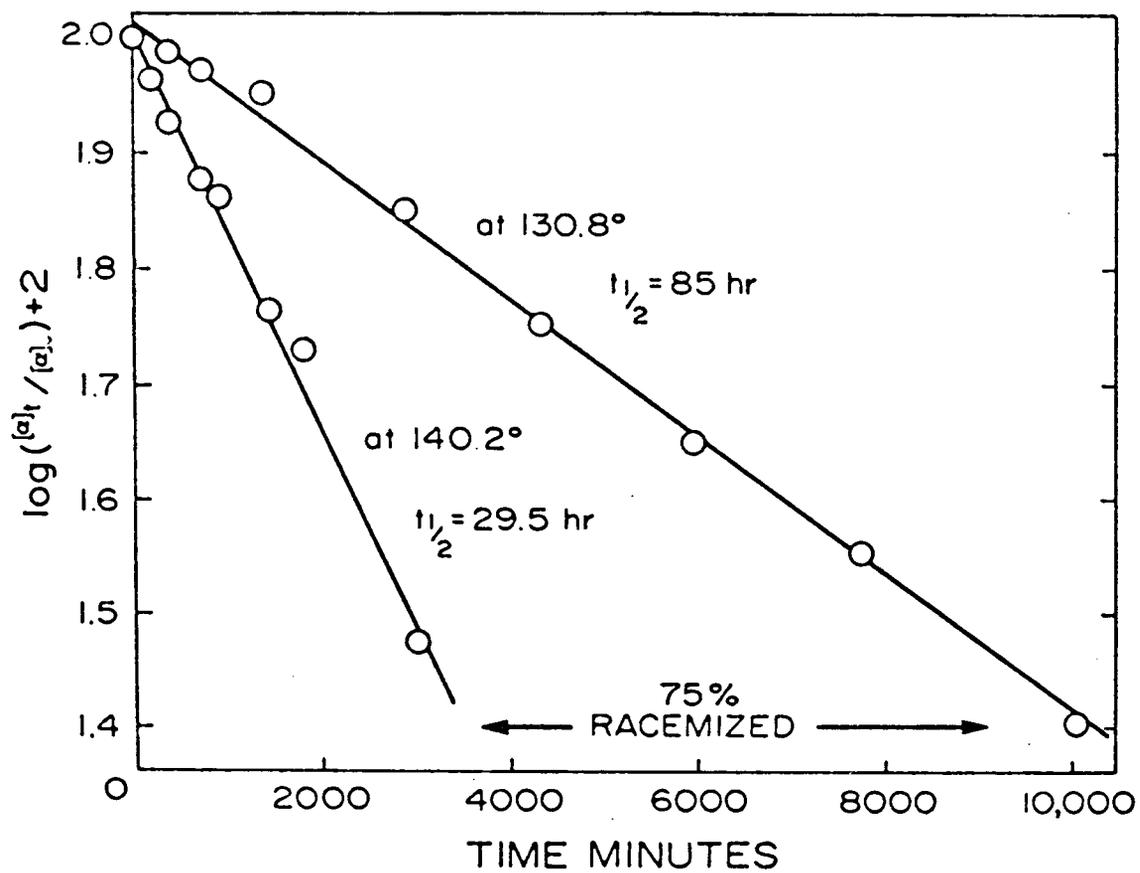


Figure 3. First-order kinetic plots for racemization of neat, polycrystalline (+)-29 in the solid phase.

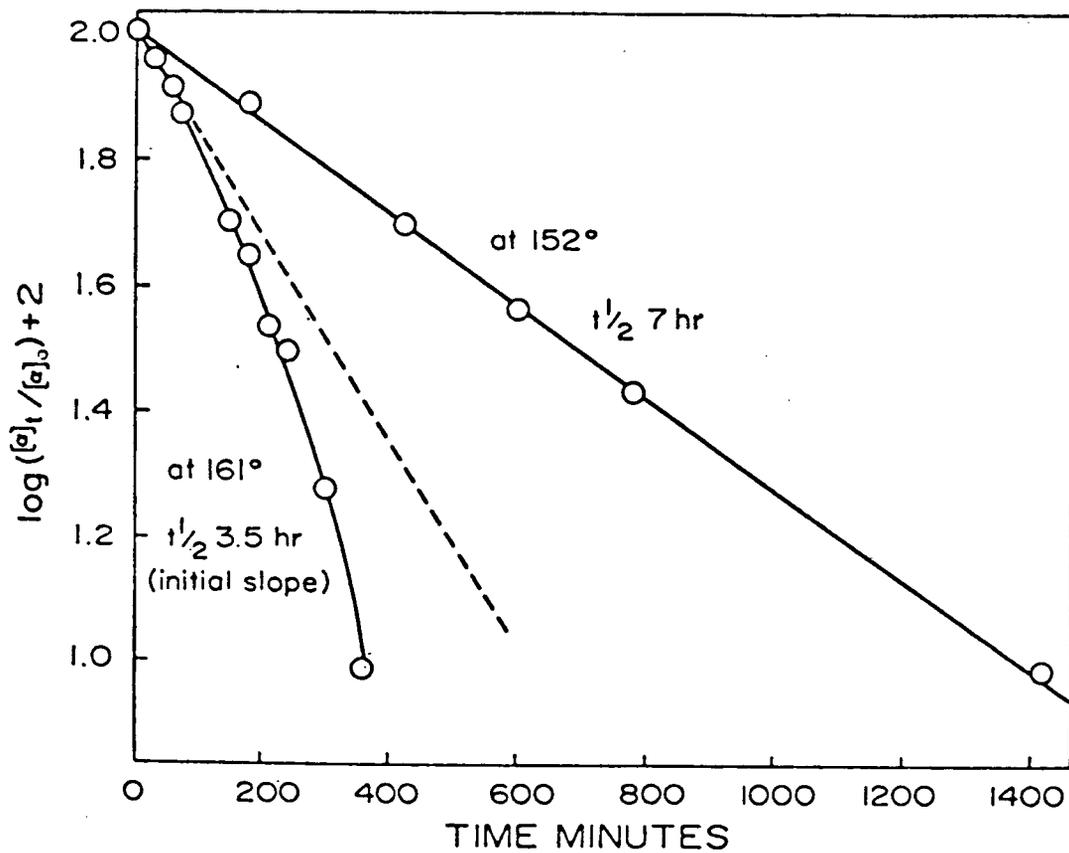


Figure 4. First-order kinetic plots for racemization of neat, polycrystalline (+)-29 at 152° in the solid phase and at 161° where melt \rightleftharpoons solid.

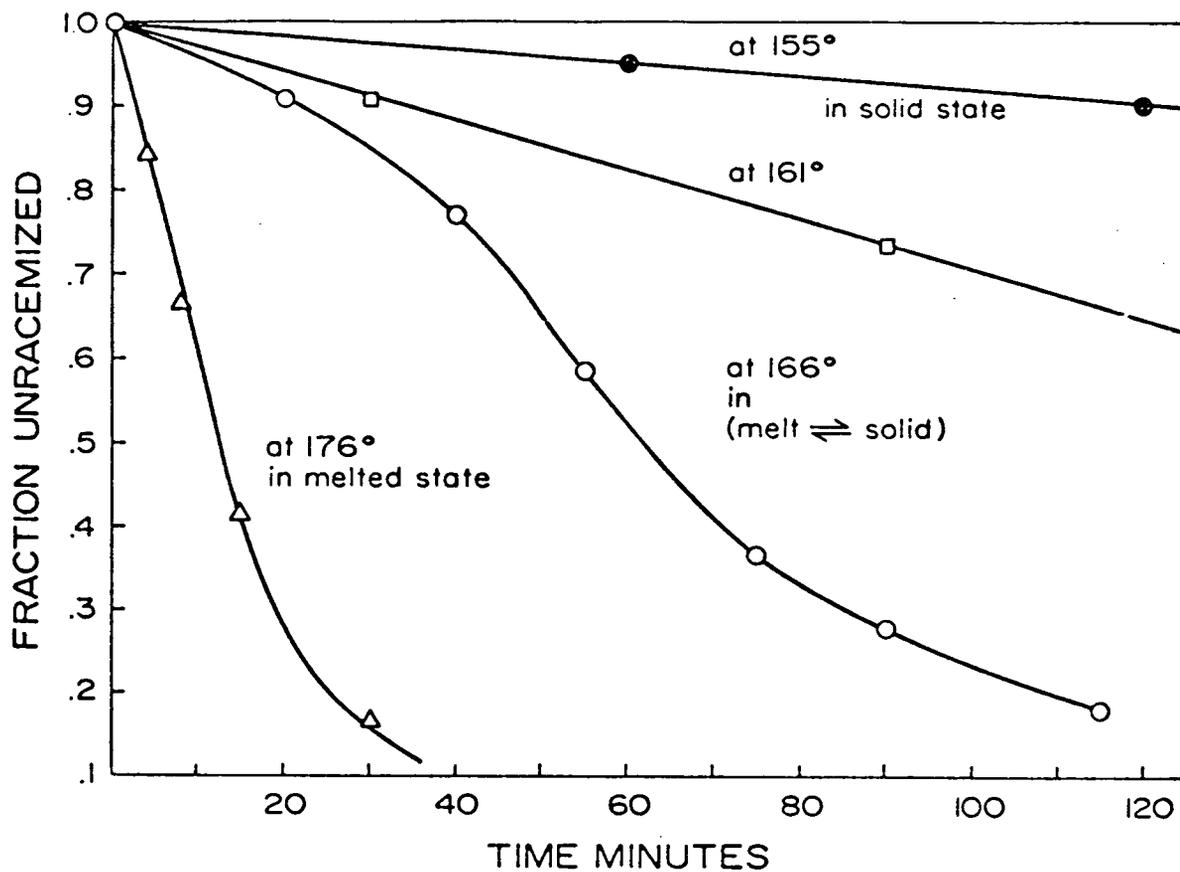


Figure 5. Kinetic data for racemization of neat samples of (+)-29 in the solid (155°), in the biphasic melt + solid system (166°), and in a completely melted system (at 176°).

was quite evident in the fraction unracemized vs. time plots at these two temperatures (Figure 5 at 166°). The log plots deviated from linearity (Fig. 4 at 161°). Rate constants were, however, obtained from the initial slopes of the log plots (Table I) for comparison to the observed first-order constants from lower temperature runs. Significant yellowing of the samples occurred, much more rapidly than with the melt reaction at temperatures as high as 194°. Some sintering indicated partial melting.

2.3 The Phase Diagram

2.3.1 The Determination of the Phase Diagram

In order to interpret correctly the kinetic results below the melting point, it was necessary to ascertain the temperature below which the system of enantiomers is totally solid. To this end, the binary phase diagram was determined using differential scanning calorimetry and X-ray powder diffraction.

In general there are only three types of binary phase diagrams formed between enantiomers.^{45a,46} These are the simple eutectic, the formation of a "phase rule" compound, and formation of a solid solution at all compositions. In the simple eutectic the crystal form of one enantiomer does not accommodate the other^c and the racemic modification is a two-phase mixture of individual crystals of pure enantiomers. The "phase rule" compound diagram is similar in that crystalline forms are immiscible, but the racemic modification is a single phase (the racemate) containing both enantiomers in a 1:1 ratio. In the solid^c except at the extreme edges of the diagram.

solution type of diagram, the crystal lattice of one enantiomer can contain the other in all proportions, and a single solid phase exists at all compositions.

The single observation that the racemic diacid 29 melts higher than the resolved material immediately restricts the choices of diagrams to two: (a) formation of a phase rule compound or (b) formation of a solid solution melting higher when racemic than when resolved.

The choice between these two is easily made with the differential scanning calorimeter (d.s.c.). The method⁴⁷ is a nonequilibrium one, and can be used to measure phase changes which are rapid, such as melting or fast solid-solid transitions. The procedure involves heating a small amount of sample in a pan and an empty reference pan at a constant rate. Any energy release or absorption in the sample is compensated by the calorimeter so that the area of the recorded peak is directly proportional to the enthalpy of the transition. Transition temperatures are easily determined once the d.s.c. is calibrated.

Samples of the diacid 29 ranging in specific rotation from +137° to 0° were heated on the d.s.c. and the temperatures and enthalpies of transition were determined. Some representative d.s.c. traces are shown in Figure 6. The resolved and racemic diacid 29 gave no peaks from room temperature up to the respective melting points (176° and 186°), where sharp endotherms were recorded. The enthalpies of fusion (ΔH_{fusion}) were $5.38 \pm 0.16 \text{ kcal mole}^{-1}$ ($29.5 \pm 0.9 \text{ cal g}^{-1}$) for the (+) enantiomer 29 and $7.13 \pm 0.24 \text{ kcal mole}^{-1}$ ($39 \pm 1.3 \text{ cal g}^{-1}$) for the racemic material. The corresponding entropies of fusion were calculated from:

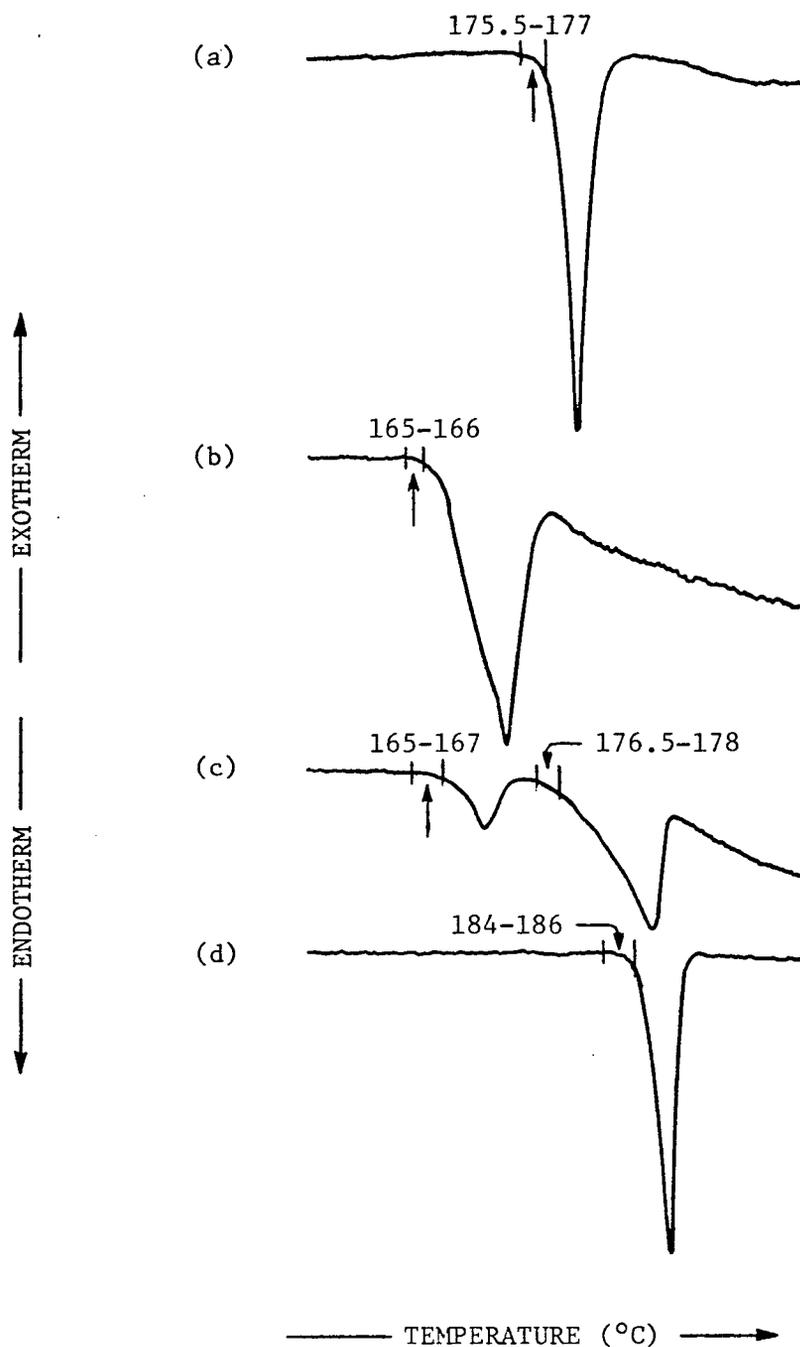


Figure 6. Differential scanning calorimeter traces (programming rate: 10 deg min^{-1}) for the diacid 29 at various compositions: (a) 0%, (b) 24.8%, (c) 45.2%, and (d) 50% (-)-enantiomer.

$$[3] \quad \Delta S_{\text{fusion}} = \frac{\Delta H_{\text{fusion}}}{T_{\text{m.p.}}}$$

which holds only at the melting point where the free energies of solid and melt are identical. The ΔS_{fusion} for the resolved diacid 29 was $12.0 \pm 0.3 \text{ cal deg}^{-1} \text{ mole}^{-1}$ and for the racemic diacid, $15.5 \pm 0.5 \text{ cal deg}^{-1} \text{ mole}^{-1}$.

Samples intermediate in activity, however, gave a single endotherm at 165° , sometimes followed by a second endotherm at slightly higher temperatures. The endotherm at 165° in samples having a range of compositions strongly implies that this is a eutectic temperature. The endotherm is largest for a sample having a specific rotation of $+68^\circ$. These observations are those expected for a phase system with racemic compound formation. A eutectic point (temperature: 165° , composition: half resolved) exists between the resolved and racemic diacid 29.

The temperatures at which the d.s.c. peaks appeared are plotted in Figure 7. The appearance of a second endotherm for some samples is consistent with the phase system.^{48,49a} At appropriate compositions, these samples will partly melt at the invariant eutectic temperature, then finish melting over a range of temperatures from the eutectic to the liquidus curve. The appearance of a second peak indicates the maximum rate of this secondary melting. The point at which the second peak returns to the base line is sometimes taken as the position of the liquidus curve,⁴⁸ but in our samples the melt was too volatile to allow a precise determination of this point. For completeness, the liquidus curves have been sketched in the phase diagram (dotted lines).

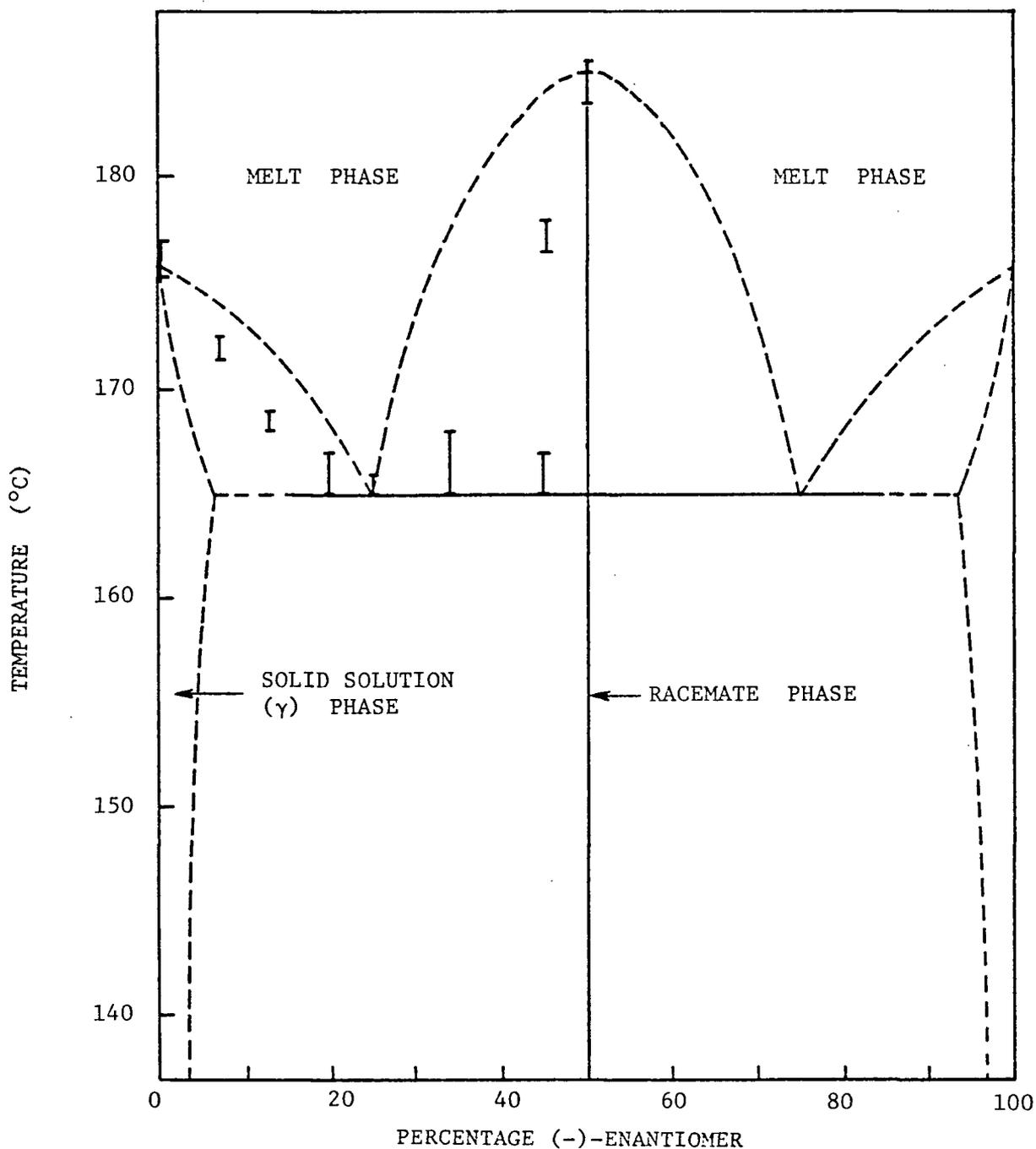


Figure 7. Phase relationship of mixtures of (+)- and (-)-enantiomers of compound 29. Vertical bars indicate the uncertainties in transition temperatures (taken at the beginning of d.s.c. endotherms). Undetermined phase boundaries (dotted lines) are estimated for completeness.

Also drawn in is a terminal solid solution, γ , which must exist,^{50,51} but may have a composition range which is small and difficult to determine with the d.s.c. The second half of the diagram ((-)-side) is a mirror image of the (+) side, and is shown in Figure 7 for completeness. The (-)-enantiomer 29 was not isolated.

The d.s.c. results were verified by X-ray powder photography. Photographs of the resolved acid were different from those of the racemate. A sample which had been half racemized showed both sets of characteristic diffraction rings, and no others. There are therefore two solid phases at this composition. No metastable intermediate phases are formed during the reaction.

2.3.2 The Identification and Stability of Reactive Phases

Knowing the phase diagram (Figure 7), we are now able to consider the phases in which racemization occurs. From 130° to 155°, only solid phases are involved in the first-order reaction. As racemization proceeds, an unreactive racemate separates from the reactive solid (+)-enantiomer.

Between the eutectic temperature and the melting points concerned, the melt and solid coexist, and reaction occurs simultaneously in both phases. Solid samples will eventually melt when held at temperatures in this range. As racemization proceeds, the liquid phase grows in volume at the expense of the solid phase. It can be shown³⁷ that a first order reaction in a disappearing solid phase combined with a faster reaction in a growing melted phase, will give rise to

an S-shaped kinetic curve. Such curves are observed in runs at 161° ^d and 166° (Figure 4,5). The individual contributions of solid and melted phase reactions can, in principle, be separated.³⁷ However, in this case the availability of kinetic data at temperatures where the system is totally melted or totally solid makes such a separation unnecessary.

Our use of the phase diagram to chart the course of a chemical reaction should perhaps be explained more fully. The meaning of such a diagram is not entirely clear from the discussion this far, since the phases described are not in chemical equilibrium.

Systems of dynamically interconverting isomers such as the enantiomeric diacids 29 are treated in standard texts on phase equilibria as "pseudobinary systems".^{45b,52} This term means that strictly under equilibrium conditions, the system would behave as a single component. However, under nonequilibrium conditions (such as with a d.s.c.) it is possible to determine a binary phase diagram. The necessary condition here is that the composition of the sample should not change during the time taken for the experiment. In this case, at the usual d.s.c. heating rates ($10^{\circ}/\text{min}$), the melting region is covered in less than two minutes, during which time very little racemization occurs (Figure 5).

The methods for determining such "nonequilibrium" phase diagrams seem well understood,⁵² but the meaning of such diagrams becomes clearer from the point of view of free energy. Consider first of all a

^d

Although 161° is below the binary eutectic, the relatively rapid darkening of samples indicates that other components are formed. These can lower the binary eutectic temperature,⁵³ causing the appearance of a liquid phase.

two-component system of isomers, with no possible isomerization reaction. At constant pressure, the free energy of each phase will be a function of temperature and composition. A three-dimensional plot of temperature - composition-free energy will therefore consist of individual free energy surfaces - one for each phase - suspended over the temperature-composition plane (i.e. the phase diagram). The stable phase (or phases) at each point on the diagram is determined by the lowest free energy surface (or combination of surfaces)^{50,51} above that point. Hence the equilibrium phase diagram is generated. If the phases at every point are always the most stable ones (i.e. all phase changes are rapid), then all points on the phase diagram are attainable experimentally.

Now let us allow for the interconversion of components. Even though the phases are reactive, all will have individual free energy surfaces as before. It still, therefore, makes sense to speak of the lowest-lying free energy surfaces, but the phase diagram which these determine is not an equilibrium diagram. For example, the melting point of a pure isomer^e can be defined as the temperature at which the free energies of the pure solid and pure liquid isomer are equal, but such a point is not in equilibrium. The system can lower its free energy further by changing its composition until final chemical equilibrium is reached. If the phases existing at any temperature and composition are always those having the lowest free energies at that point, then the phase changes are fast. The diagram can then be determined experimentally, provided the isomerization reaction

^e Such a point has been called an "ideal constant" and the pseudobinary system has been referred to as a system in "false equilibrium"^{45b} but the relationship to free energy surfaces, although implied, should be explicitly stated.

is sufficiently slow. If the reaction is too fast, some points, such as the pure isomer melting points, may be impossible to attain (see Section 3.3.2.1).

In this manner, by assuming that phase changes are more rapid than the isomerization, the course of a reaction may be mapped on a phase diagram. For example, when a reaction is "passing through" a two-phase solid + melt region at constant temperature and pressure, the composition of the solid and melt phases will be constant and equal to the solidus and liquidus compositions. Such an approach is basic to our treatment of reactions in neat organic materials.

2.4 Mechanism in the Solid State

In view of the many complexities associated with reactions in the solid state^f the kinetic simplicity of this racemization is surprising. Reactions in organic solids commonly show induction periods,⁵⁵ autocatalytic effects,⁵⁶ or a dependence on aging and on particle size.⁵⁷ All of these features are conspicuously absent below the eutectic of the system of enantiomers which we have studied.

The first-order kinetics mean that the rate-determining step in the solid-state racemization can occur with equal probability at any point in the polycrystalline solid. That is, the location of the diacid molecules 29 (whether they are at the edges of crystallites, at defects or dislocations, or deeply imbedded in a region of perfect lattice) makes no difference to their reactivity. Consistent with this is the

^f A collection of papers dealing generally with reactions in solids may be found in the published symposia on the Reactivity of Solids.⁵⁴

observation that grinding or use of different batch preparations has no effect on the kinetic results. In these different samples there will be a widely different polycrystalline grain size and defect or dislocation density in the reactant.

The reaction is also not catalyzed by the presence of the product (racemic compound). As the product phase grows, the reactant-product interface will increase, pass through a maximum, then decrease as the reactant disappears. In some organic decompositions,⁵⁶ the developing product surface causes acceleration of the reaction and the production of sigmoid-shaped kinetic curves. In our system, maximum rate occurs at the beginning of the solid reaction. Such a rate maximum is not due to a very short acceleration period and the presence of product phase, because X-ray results clearly show only the pure enantiomer at the start of the reaction.

Therefore, the necessity of having to grow a product phase from a reactant cannot control the racemization reaction. The change of phase associated with the reaction must be fast compared to the rate-determining step.^g

Consideration will now be given to the nature of the rate-determining step. In the melt, the racemization will consist of a reversible first-order reaction:

^g There is one specialized case of first-order kinetics in a reaction controlled by a phase change. Some inorganic decompositions show first-order behaviour because of a very fine particle size.⁵⁸ However, the solid-state reaction of the diacid 29 is independent of the state of subdivision of the solid, so that our observed first-order kinetics are not due to this effect.

C represents the product compound, which is considered as a hydrogen bonded pair of enantiomers. All species are first contained in the γ phase (Figure 7). At low conversions, the first products formed from a first-order process in a single reactant phase would exist in solid solution with the reactant, since a sufficiently small number of product molecules randomly scattered throughout the reactant matrix could not form a separate phase.^h As reaction proceeds, the reactant phase would eventually become supersaturated in product, and unstable with respect to a two-phase reactant-product system. The last reaction therefore shows the compound C separating (relatively quickly, as discussed above) from the γ phase.

The reversible interconversion of enantiomers will not have equal rate constants (i.e., $k_3 \neq k_4$) in the γ phase as is the case in the melt phase. The γ crystals will present a dissymmetric environment to the enantiomer B, causing a difference in the free energies of A and B in the γ phase. The addition of B enantiomer to pure A will first lower^{50,51} then raise the total free energy of the γ phase (see Figure 8 (a)). The free energies of the species B and C relative to A are shown schematically in Figure 8 (b). B and C are at a higher energy than A because they are not expected to fit into the γ lattice as easily as A. The first pair of rate constants will therefore likely be ordered $k_3 < k_4$. Once a B molecule is formed, it will be surrounded with A molecules, and will probably be easily able to move into position to form hydrogen bonds with A, thereby creating compound C. If this

^h In some photodimerizations, the product is considerably soluble in the reactant lattice.⁴

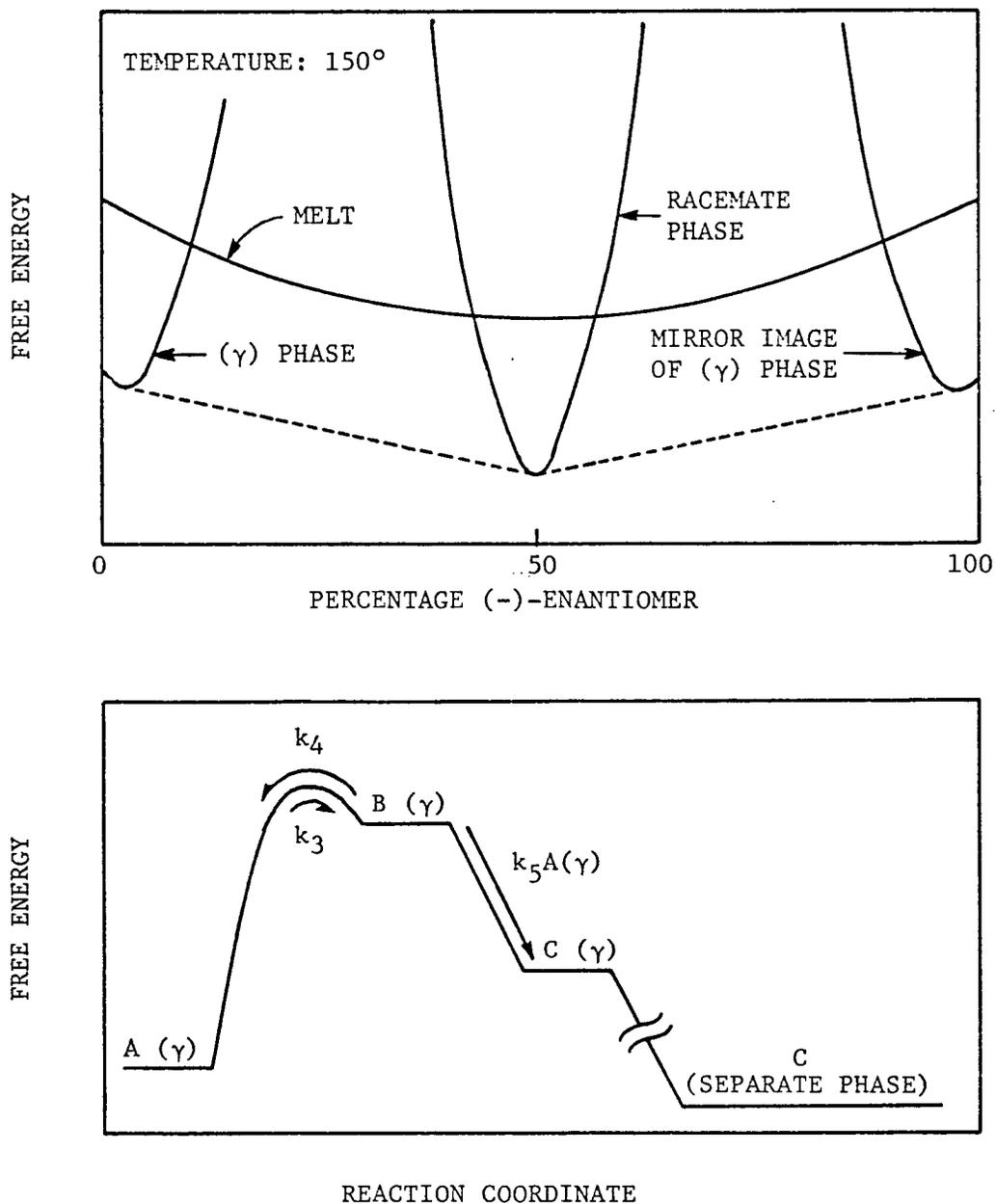


Figure 8. (a) Schematic free energy-composition plot in the phase system (+)- and (-)-29, at constant pressure (atmospheric) and temperature (150°). The dotted lines show the lowest free energy surfaces for the two-phase regions.

(b) Schematic free energy-reaction coordinate plot for the solid-state racemization of (+)-29 (shown as A (γ)) at 150°.

reaction is fast, then perhaps k_5 will be sufficiently large to allow $k_4 \ll k_5 A(\gamma)$ throughout most of the reaction. ($A(\gamma)$ is the mole fraction of total diacid which is A and in γ . This quantity is unity at the beginning of the racemization, and zero at the end.) The rate equation for the disappearance of $A(\gamma)$ is:

$$[4] \quad - \frac{dA(\gamma)}{dt} = k_3 A(\gamma) - k_4 B(\gamma) + k_5 A(\gamma) B(\gamma)$$

and if $k_3 < k_4 \ll k_5 A(\gamma)$, $B(\gamma)$ is a short-lived reactive intermediate in the γ phase. A steady-state treatment on $B(\gamma)$ gives:

$$[5] \quad \frac{dB(\gamma)}{dt} = 0 = k_3 A(\gamma) - k_4 B(\gamma) - k_5 A(\gamma) B(\gamma)$$

$$B(\gamma) = \frac{k_3 A(\gamma)}{k_4 + k_5 A(\gamma)} \approx \frac{k_3}{k_5}$$

Substitution of [5] into [4] yields:

$$[6] \quad - \frac{dA(\gamma)}{dt} = k_3 A(\gamma) - \frac{k_4 k_3}{k_5} + k_3 A(\gamma) \approx 2k_3 A(\gamma)$$

Integration will give the result $k_{\text{obs}}(\text{solid}) = 2k_3$. Therefore, the above assumptions about the relative magnitudes of the rate constants lead to the conclusion that as soon as one A converts to B, another immediately disappears in the formation of C.

As with the melt reaction, the substitution of $k_{\text{obs}}(\text{solid}) = 2k_3$ in Equation 1 (p 20) does not alter ΔH^\ddagger for the solid, and changes the calculated ΔS^\ddagger only by a small amount ($1.4 \text{ cal deg}^{-1} \text{ mole}^{-1}$).

The activation parameters describe the same process in the melt as in the solid - the reverse Diels-Alder reaction and recombination to form the enantiomer - and can be compared for the two phases. Although the free energies of activation are close (Table II), the calculated ΔH^\ddagger and ΔS^\ddagger are markedly different. Passage of the adduct from the ground state to the transition state apparently involves an entropy increase (a local disruption in the highly ordered crystal lattice), at the cost of a higher energy of activation than in the melt.

The similarity of rate constants in the solid and melt ($k_{\text{obs}}(\text{melt})/k_{\text{obs}}(\text{solid}) \approx 5$ at 150°C) is rather surprising considering that the few examples in which this comparison can be made show much larger ratios (ca. 10^3 - 10^4).^{2a} However, the endo cyclopentadiene-maleic anhydride adduct 27 (p 15) also has a facile solid-state isomerization but this reactivity can be attributed to a plastic crystalline solid state.³⁷ Such mobile solids are characterized by a low entropy of fusion (ca. $5 \text{ cal deg}^{-1} \text{ mole}^{-1}$),^{59a} much smaller than the entropy of fusion observed ($12 \text{ cal deg}^{-1} \text{ mole}^{-1}$) for the (+)-cyclopentadiene-fumaric acid adduct 29, reported here. Unlike the endo anhydride 27, there is therefore a distinct energy difference between the (+)-diacid 29 in the melt and in the solid state.

Several years ago Hinshelwood⁶⁰ considered this energy difference in relation to the rate constants in both states. Assuming that the transition state is the same in both solid and melt, he suggested that the rate difference might be related quantitatively to the enthalpy of fusion:

$$[7] \quad \ln \frac{k(\text{melt})}{k(\text{solid})} = \frac{\Delta H_{\text{fusion}}}{RT}$$

However, substitution of our determined ΔH_{fusion} (5.38 kcal mole⁻¹) leads to a ratio of $k(\text{melt})/k(\text{solid})$ of 6×10^2 at 150°, considerably greater than the observed factor of 5. An improved relationship considers the free energy difference in the ground state³⁷ (i.e., accounts for both enthalpy and entropy differences):

$$[8] \quad \ln \frac{k(\text{melt})}{k(\text{solid})} = \frac{G(\text{melt}) - G(\text{solid})}{RT}$$

Near the melting point, the free energy difference between the phases can be approximated by the enthalpy and entropy of fusion:⁶¹

$$[9] \quad \ln \frac{k(\text{melt})}{k(\text{solid})} = \frac{\Delta H_{\text{fusion}}}{RT} - \frac{\Delta S_{\text{fusion}}}{R}$$

$$= \frac{\Delta H_{\text{fusion}}}{R} \left(\frac{1}{T} - \frac{1}{T_{\text{m.p.}}} \right)$$

where the relation $\Delta S_{\text{fusion}} = \Delta H_{\text{fusion}}/T_{\text{m.p.}}$ (Equation 3, p 30) has been taken into the equation. Substituting $\Delta H_{\text{fusion}} = 5.38$ kcal mole⁻¹ yields $k(\text{melt})/k(\text{solid}) = 1.5$ at 150°, considerably closer to the observed ratio of 5.

In the above discussion, the rate difference was taken as a reflection of the difference in ground state free energies only. In general, however, both the transition and ground states in the solid reaction may be different from those in the liquid state. The restrictions imposed on the reacting molecule in the solid state can

be likened to a cage effect. The addends (cyclopentadiene and fumaric acid) produced as intermediates in the reverse Diels-Alder reaction will be held in position by the surrounding lattice rather than diffusing apart. If the restriction is severe enough, such a cage effect could be stereospecific; in this case stereospecificity would be revealed in a reduced rate of racemization in the solid, since the dissociated addends would retain orientation. Since rate retardation is only slight, such a mechanism is essentially inoperative. Rather, the addends are free to rotate quickly and recombine, forming the enantiomer 29.

2.5 Conclusion

This solid-state reaction indicates that certain thermal reorganization reactions may not be appreciably kinetically hindered in the solid state. The higher energy needed to approach a transition state in a crystal lattice can be offset partially by a favourable entropy of activation, facilitating the solid-state reaction.

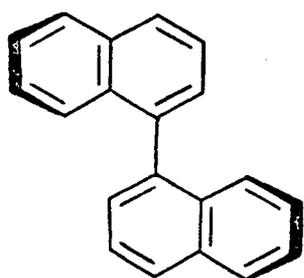
Reactions in solids can be kinetically simple even though a phase change occurs during reaction. Examples of first-order reactions in neat organic solids^{37,62} are rare, but this is perhaps only a reflection on the small number of systems that have been studied from a kinetic standpoint.

Observation in single crystals of a product phase appearing at defects, dislocations or interfaces^{24,63} does not necessarily indicate that reaction occurs at such sites. Instead, it may mean that the product has already been formed by a simple process inside the reactant

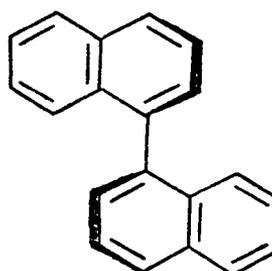
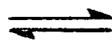
crystal, and is only separating out at such irregularities. Kinetic studies with polycrystalline samples can be used to differentiate between the two possibilities.

3 RESOLUTION OF RACEMIC 1,1'-BINAPHTHYL IN THE SOLID STATE

The compound 1,1'-binaphthyl is one of the simplest chiral hydrocarbons. Its dissymmetry is molecular in nature, and enantiomer interconversion is possible simply by rotation about the interannular bond, rather than by any bond-breaking process. The rotation is sufficiently restricted to allow isolation of either enantiomer. First resolved in 1961, S-(+)-1,1'-binaphthyl has been used in solution racemization studies.⁶⁴⁻⁶⁶ The half-life for racemization in several solvents is ca. 15 min at 50°. Recently, R-(-)-1,1'-binaphthyl was also resolved and studied in solution.⁶⁷ The absolute configuration of 1,1'-binaphthyl was deduced from a crystallographic study in 1968.⁶⁸



R-(-)-1,1'-Binaphthyl



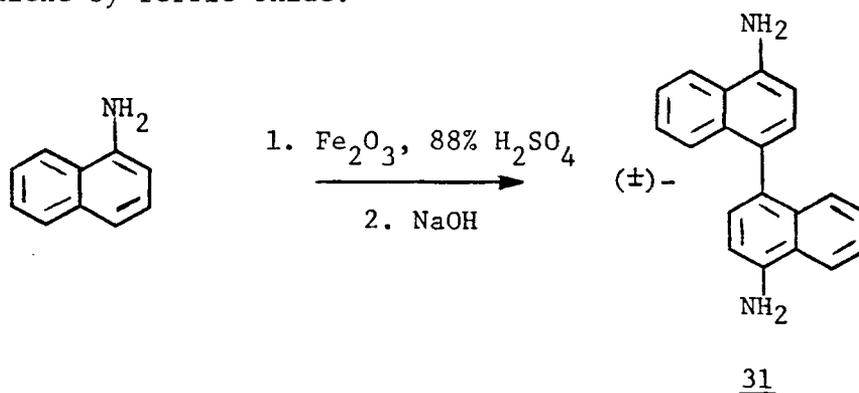
S-(+)-1,1'-Binaphthyl

3.1 The Preparation of 1,1'-Binaphthyl

3.1.1. S-(+)-1,1'-Binaphthyl from the Diastereomeric Resolution of Racemic Naphthidine

S-(+)-1,1'-Binaphthyl has been successfully resolved via the (+)-naphthidine precursor.^{64,65} We therefore began our preparation of optically active 1,1'-binaphthyl by synthesizing racemic naphthidine (31).

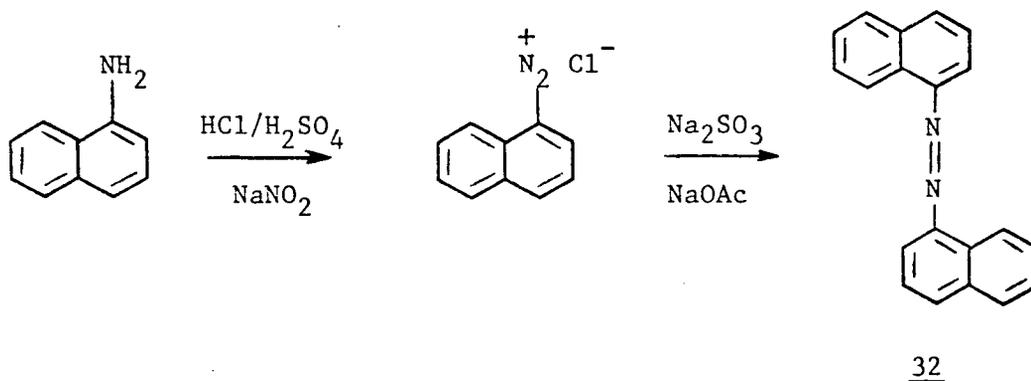
The first preparation of naphthidine which we attempted was that given by Sah and Yuin.⁶⁹ It involved the oxidative coupling of 1-aminonaphthalene by ferric oxide:



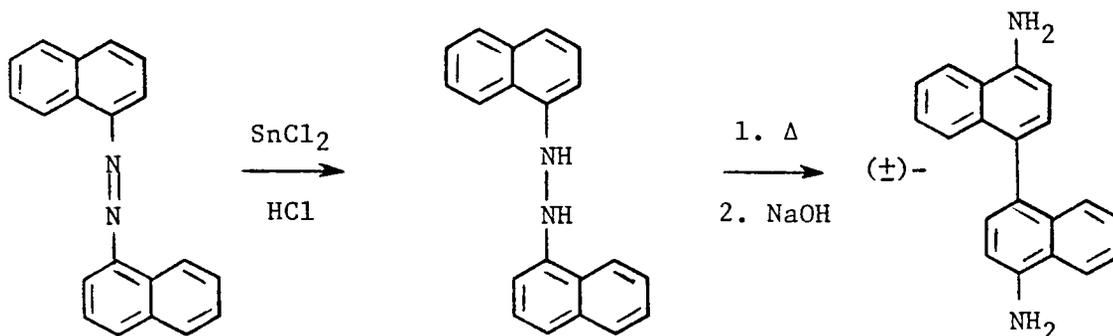
The reported yield of purified naphthidine was 60%. However, in our hands the method gave poor yields (<10%) of naphthidine, and the procedure was abandoned in favour of another which seemed more promising.

This second preparative route was developed by Cohen and Oesper.⁷⁰ 1-Aminonaphthalene was diazotized then reductively coupled to form azonaphthalene (32), which was isolated in a crude form. The azonaphthalene was suspended in boiling ethanol and reduced with stannous chloride in hydrochloric acid to hydrazonaphthalene, which immediately rearranged to naphthidine hydrochloride. Treatment with sodium hydroxide regenerates the free base. The yield of recrystallized

naphthidine was stated as 33.5%. The procedure worked well, and we were

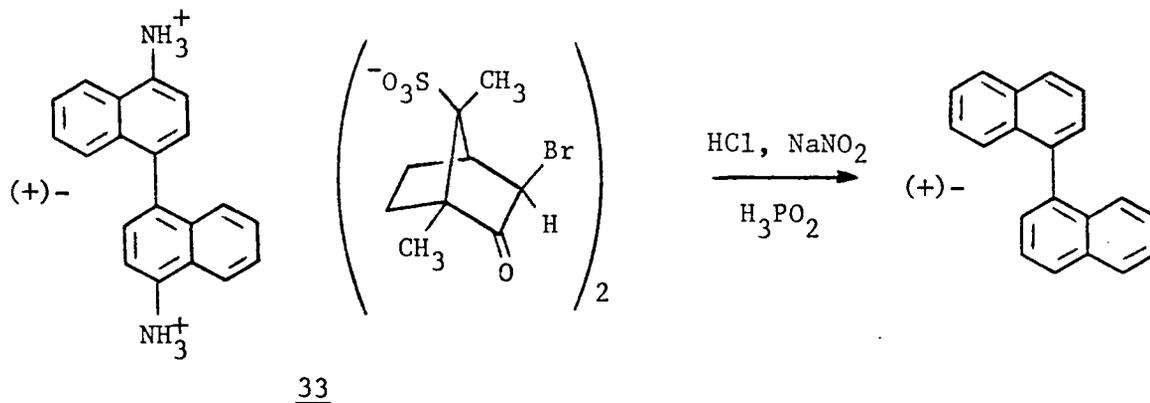


able to prepare 45 g of pure naphthidine (m.p. 201-202°) by repeating the sequence eight times. Average yield of the last five preparations was 26%.



Racemic naphthidine was then resolved by forming the salt with (+)-ammonium α -bromo-D-camphor- π -sulfonate. Theilacker and Hopp⁷¹ have performed this resolution. Use of two moles of resolving agent for each mole of naphthidine gave 65% material after recrystallization from ethanol-water. We carried this resolution as far as the salt 33, obtaining the material in somewhat lower yields but comparable specific rotations ($[\alpha] = +80^\circ$).

The (+)-naphthidine α -bromo-D-camphor- π -sulfonate salt (33) can be directly deaminated to S-(+)-1,1'-binaphthyl, without having to isolate

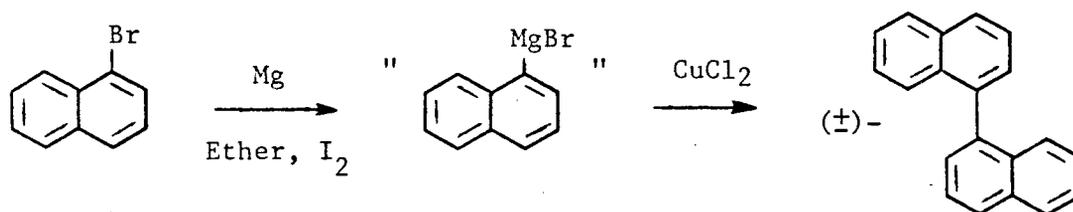


free (+)-naphthidine. This procedure was devised by Colter and Clemens,⁶⁵ and gave (+)-1,1'-binaphthyl ($[\alpha] = +145-165^\circ$) in 40-55% yield. We adopted this method, with a slightly modified purification procedure, and were able to obtain S-(+)-1,1'-binaphthyl ($[\alpha] = +97^\circ$) in 55% yield.

3.1.2 Racemic 1,1'-Binaphthyl from Optically Inactive Reagents

In order to characterize fully the phase system formed between resolved and racemic binaphthyl (or, more correctly, between R- and S-1,1'-binaphthyl enantiomers), some racemic 1,1'-binaphthyl was prepared.

The preparation followed was that of Sakellarios and Kyrimis.⁷² The Grignard reagent from 1-bromonaphthalene was coupled by cupric chloride, forming 1,1'-binaphthyl:



The reaction proceeded easily, and starting materials were readily available, so that large quantities of racemic 1,1'-binaphthyl could be obtained (our yield of purified binaphthyl was 20%).

3.2 Discovery of the Solid-State Resolution¹¹¹

Having obtained some 1,1'-binaphthyl which was optically active, we then prepared to look for any racemization below the melting point (158°) of the solid. Since there was good evidence⁷³ for the existence of two crystalline forms of 1,1'-binaphthyl (m.p. 145° and 158°), it was of interest to check for racemization in both forms. These "low-melting" and "high-melting" forms could be obtained by slow and fast recrystallizations, respectively, from petroleum ether (b.p. 30-60°).⁷³ Accordingly, half of the prepared optically active 1,1'-binaphthyl ($[\alpha] = +97^\circ$) was recrystallized rapidly (giving crystals of $[\alpha] = +99^\circ$), and half slowly (giving material with $[\alpha] = +79^\circ$) from pentane. At the boiling point of pentane (36°) a little racemization of the dissolved 1,1'-binaphthyl will occur.⁶⁶

Our initial check for the presence of any solid-state racemization was to heat 20 mg of the polycrystalline 1,1'-binaphthyl sample with activity $[\alpha] = +99^\circ$ for one hour at 120°. When the sealed ampule was opened and analyzed, the specific rotation was $[\alpha] = +108^\circ$. Racemization had not occurred, and the apparent increase in rotation caused us to check the precision of the polarimetric method of analysis. It was learned that the figure should be correct to within $\pm 2^\circ$. The increase therefore seemed genuine, but needed verification. A second sample of the same material was therefore heated, along with a sample of $[\alpha] = +79^\circ$

material, for 36 h at 120°. Analysis showed that the latter had not changed at all from $[\alpha] = +79^\circ$, but the original material had increased from $[\alpha] = +99^\circ$ to $+114^\circ$. Even after such prolonged heating the sample remained a white, crystalline solid and gave the single 1,1'-binaphthyl peak when analyzed by gas-liquid chromatography. The binaphthyl was evidently resolving, not racemizing, in the solid state.

This incredible result was soon verified rather dramatically. In order to find the range of temperatures in which this phenomenon might occur, the second temperature chosen was 150°, nearer the higher melting point of 158°. Samples of both batches of optically active 1,1'-binaphthyl, along with some control samples of racemic 1,1'-binaphthyl (which had also been recrystallized rapidly and slowly from pentane) were heated for various lengths of time (Table III). The original (fast recrystallized) sample of active 1,1'-binaphthyl increased steadily from $[\alpha] = +99^\circ$ to $+163^\circ$ over a period of 2.5 days. Samples from the slowly recrystallized batch, which had remained at $[\alpha] = +79^\circ$ at 120°, increased to $[\alpha] = +205^\circ$ within two hours and remained at this rotation for 2.5 days. The racemic sample which had been recrystallized quickly remained at $[\alpha] = 0^\circ$ throughout. However, the slowly recrystallized racemic sample, surprisingly, developed optical activity. Rotations were somewhat scattered, but all eleven individual samples were positive. This self-resolution of 1,1'-binaphthyl can apparently occur even in material which is racemic ($[\alpha] = 0.0 \pm 0.5^\circ$).

This unusual behaviour of solid 1,1'-binaphthyl prompted a search for a method of preparing batches of binaphthyl which would resolve to a high rotation from a low initial rotation simply on heating. Since all

Table III

Summary of Initial Investigations of the Development of Optical Activity
in Neat, Polycrystalline 1,1'-Binaphthyl

1,1'-Binaphthyl Used	Temperature, °C	Time, hours	[α], degrees
^a Material of [α] = +99°	120	1	+108
"	"	36	+114
"	149.6	1	+126
"	"	2	+130, +129 ^c
"	"	5	+135, +133 ^c
"	"	24	+157, +152 ^c
"	"	63.5	+163
^b Material of [α] = +79°	120	36	+79
"	149.6	1	+105
"	"	2	+193, +205 ^c
"	"	5	+208, +206 ^c
"	"	24	+208, +210 ^c
"	"	63.5	+207
^a Racemic Batch A	149.6	12.5	0, 0 ^c
"	"	37.5	0, 0 ^c
"	"	63.5	0
^b Racemic Batch B	149.6	0.017	+4
"	"	0.083	+41, +47 ^c
"	"	0.5	+98, +90 ^c
"	"	1.0	+79

(Table III, continued)

Racemic Batch B, continued	149.6	12.5	+119, +79 ^c
"	"	37.5	+93, +83
"	"	63.5	+97

^a From a fast recrystallization (pentane).

^b From a slow recrystallization (pentane).

^c Specific rotations of two individual samples heated for the same length of time at the same temperature.

solid samples of 1,1'-binaphthyl had been recrystallized, the next several weeks were devoted to trying to develop a method of recrystallizing racemic or partially active 1,1'-binaphthyl "successfully" from pentane. Variations were made in the rate of recrystallization, the concentration of 1,1'-binaphthyl in the pentane solvent, and the method of seeding. No deliberate attempt was made to add seeds of foreign dissymmetric material; it was desirable to restrict the system entirely to R- and S-1,1'-binaphthyl. Once a resolvable batch (i.e., one which would increase significantly in specific rotation on heating) was obtained, however, careful repetition of the crystallization procedure would not produce a second batch which was equally as successful.

From this experimentation the following important fact was learned. All samples of 1,1'-binaphthyl, regardless of the particular method of preparation, either retained or increased specific rotation when heated in the solid state below 158°. No racemization ever occurred on heating pure, active 1,1'-binaphthyl below its melting point. Also, we observed that cooling a sample to room temperature or below then reheating did not produce any additional increment in rotation. Re-

crystallization from pentane did not cause appreciable loss of activity.

Combining these observations, we devised a cycling procedure which was capable of producing larger quantities of well-resolved 1,1'-binaphthyl. Starting with either slightly resolved 1,1'-binaphthyl or a racemic material which gained some optical activity on heating, a specific rotation at least as great as $[\alpha] = +190^\circ$ could eventually be obtained. (The limit of resolution, as we later discovered (Appendix A, p 178), is $[\alpha]_D = \pm 245^\circ$.)ⁱ First, the sample (usually ca. 1 g in size) was recrystallized from pentane. To conserve material, the pentane was removed in vacuo after the recrystallization was complete. The solid was then heated at 150° , and an increment in rotation almost always occurred. A second recrystallization of this more active material again produced crystals which could resolve even further on heating. By cycling in this manner, the optical activity of any sample of 1,1'-binaphthyl could be systematically enhanced. Racemic starting material which did not change on heating could be made to resolve by dissolving in some active material at the recrystallization stage. An example of an experiment that produced a specific rotation of $[\alpha] = +194^\circ$ in four cycles, and one giving $[\alpha] = -194^\circ$ after three cycles are shown in Table IV.^{i'}

One shortcoming of this procedure was that although some increment in rotation was assured, we were unable to predict how large it would be. Some samples would increase only a few degrees on heating; others

ⁱ The highest specific rotation at the sodium D line, 5893 \AA , reported for samples of optically active 1,1'-binaphthyl obtained by the classical resolution procedure is $[\alpha]_D = +192^\circ$.⁶⁵ Other values are $[\alpha] = +245^\circ$ at 5791 \AA ⁶⁴ and $[\alpha] = -250^\circ$ at 4360 \AA .⁶⁷

^{i'} This conversion of essentially all of a racemic material to only one enantiomer is sometimes referred to as an "asymmetric transformation,"¹¹⁰ but we prefer the more general term, "resolution."

Table IV

Examples of the Cycling of Racemic 1,1'-Binaphthyl to High Specific Rotations

Cycle Number	[α] After Recrystallization, degrees	[α] After Heating at 150°, degrees
1	0	(+41, +44) ^a
2	(+42, +44) ^a	(+109, +116) ^a
3	(+110, +112) ^a	(+186, +185) ^a
4	(+175, +179) ^a	(+197, +190) ^a
1	0	(-52, -45) ^a
2	-34	-79
3	-49 ^b	-194

^a Duplicate analyses of the batch being cycled.

^b This loss in activity on recrystallization occurred because decolourizing carbon was used in the pentane solution. 1,1'-Binaphthyl racemization in pentane is catalyzed by certain carbon blacks.⁷⁴

jumped some 150° in rotation. Therefore, the number of cycles required to achieve [α] = \pm 190-220° varied from one to greater than four in the experiments attempted.

This remarkable ability of 1,1'-binaphthyl to resolve simply on heating reflects an unusual stereospecificity in the solid state. A thorough knowledge of the phase relationships of the R- and S-1,1'-binaphthyl system is an essential part of any explanation of the

phenomenon. Our attempts to establish the nature and relative stability of the phases are reported in the following section.

3.3 Phase Diagram of the System R- and S-1,1'-Binaphthyl

3.3.1 Nature of the Phases

The low- and high-melting forms of 1,1'-binaphthyl reported by Badar et al⁷³ were also obtained in our recrystallizations of racemic and partially active material. Contrary to their observations with racemic 1,1'-binaphthyl, we found no good correlation between the rapidity of recrystallization and the form obtained.^j Both low- and high-melting forms resulted from both slow and rapid recrystallizations. Most often, mixtures of the two forms were obtained. That is, perhaps half of a sample would melt at 145°, the rest melting at 158°. Occasionally, recrystallization would yield one form with very little, if any, of the other, and these batches allowed a study of both forms.

In agreement with Badar and coworkers,⁷³ each form had a characteristic infrared spectrum when taken in a nujol mull (Figure 9). The striking difference at 769 cm⁻¹ and also the smaller differences from 940-980 cm⁻¹ reported by these investigators are quite apparent. When either form is taken into solution, these differences disappear.⁷³ The fact that the most marked difference was in the C-H out-of-plane vibration region of the spectrum led these authors to suggest that within each R or S configuration, a cis (30a) conformation might exist in one crystalline modification, and a trans (30b) conformation in the other.

^j or, as just presented, any relation to the speed of recrystallization and the ability of the material to resolve on heating.

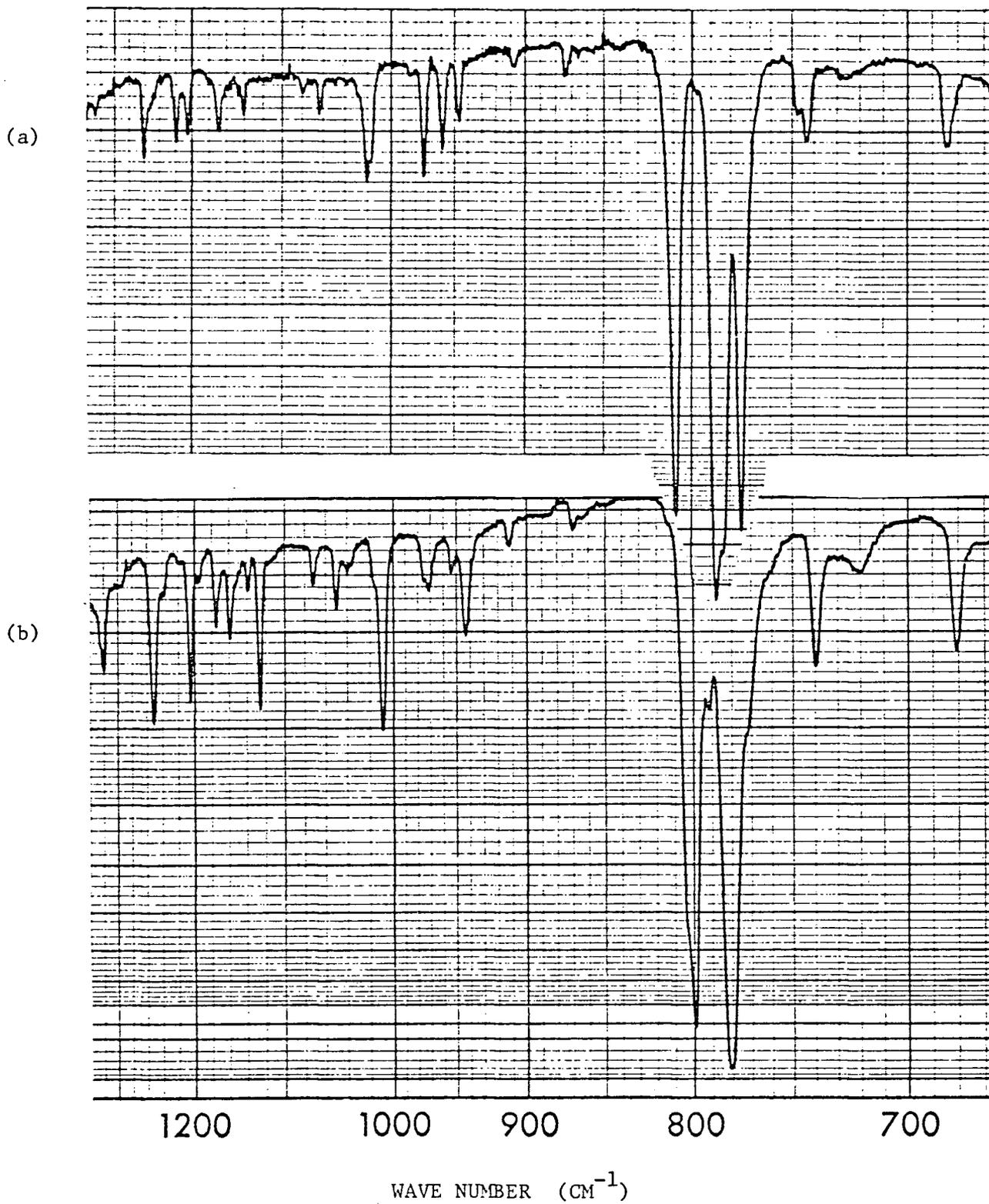
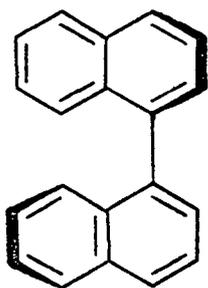
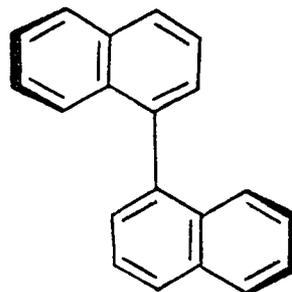


Figure 9. Infrared spectrum of 1,1'-binaphthyl (nujol mull).

(a) Low-melting form. (b) High-melting form.

30a

R-(-)-1,1'-Binaphthyl,
cis conformation

30b

R-(-)-1,1'-Binaphthyl,
trans conformation

X-Ray powder diffraction also differentiates between the two forms. Table V lists the two patterns we obtained for the low- and high-melting forms on a Debye-Scherrer powder camera, alongside a pattern for 1,1'-binaphthyl determined by Hofer *et al.*⁷⁵ For each interplanar spacing is listed the intensity of the line relative to the most intense line in the photograph (designated 100). The three strongest lines are indicated. This format is that of the American Society for Testing Materials^{76a} and allows a comparison between our results (obtained with Cu K α radiation, wavelength 1.54178 Å) and those of Hofer (obtained with Fe K α radiation, wavelength 1.93728 Å). In spite of his reported melting point (159.5-160°), there is little correspondence between our pattern for the high-melting form and the 1,1'-binaphthyl pattern of Hofer. Rather, the four strongest lines on his pattern and on ours for the low-melting form are in close agreement. Similarities among the weaker lines are difficult to find, but at these low intensities comparison is difficult because our figures represent integrated intensities whereas his are visual estimates.

Table V

X-Ray Powder Diffraction Patterns for Low-Melting (Racemate) and High-Melting (Eutectic) Forms of 1,1'-Binaphthyl

Low-Melting Form			High-Melting Form			Literature ⁷⁵	
d, Å		I/I ₁	d, Å		I/I ₁	d, Å	I/I ₁
10.1		25	6.9		10	10.2	50
5.3	3rd	45	6.4	2nd	70	6.0	25
5.0 ^a	2nd	80	5.6	3rd	55	5.4	3rd 75
4.65		5	5.0		5	5.0	2nd 80
4.07		5	4.74		50	4.66	25
3.94		20	4.39 ^a	1st	100	4.39	10
3.67	1st	100	4.07		5	4.11	50
3.14		5	3.72		70	3.98	50
2.97		20	3.46		10	3.69	1st 100
2.92		5	3.33		10	3.52	5
2.79		5	3.20		10	3.20	25
2.54		5	3.11		10	3.00	50
2.48		5	3.00		5	2.95	25
2.34		5	2.91		5	2.81	35
2.28		5	2.84		5	2.68	10
2.16		5	2.78		30	2.56	35
2.08		5	2.21		5	2.49	35
			2.03		5	2.35	25
						2.29	25
						2.25	25
						2.18	25
						2.14	25
						2.08	35
						2.04	10

^a Unresolved doublet.

The fact which is most apparent from Table V is that the patterns for the low- and high-melting forms are considerably different. The total absence of the stronger lines of one form of 1,1'-binaphthyl in the pattern of the other attests to the high "phase purity" of our samples. The low-melting form analyzed was racemic, but the high-melting form, which we could obtain in all activities (from $[\alpha] = 0$ to $\pm 245^\circ$), gave the same pattern regardless of the specific rotation of the sample analyzed.

Fortunately, a full crystallographic study of the low-melting form has recently been performed by Kerr and Robertson.⁷⁷ This crystal modification belongs to a monoclinic, centrosymmetric space group (C2/c), with lattice parameters $a = 20.98 \text{ \AA}$, $b = 6.35 \text{ \AA}$, $c = 10.13 \text{ \AA}$ and $\beta = 105.7^\circ$. There are four molecules to each unit cell, two of which have the R conformation, the others being S. The two naphthalene units in both R and S molecules are cis disposed, with an angle of 68° between them, and are very close to the dimensions of naphthalene itself. The existence of an ordered array of equal numbers of R and S molecules establishes the low-melting form as a "phase rule" compound (see Section 2.3.1, p 27) in the binary system R- and S-1,1'-binaphthyl.

Let us now consider the nature of the high-melting form. The fact that the X-ray powder photographs of this form are the same at all specific rotations eliminates a "phase rule" compound (which would have been a polymorph of the low-melting form) as a possibility.^{46, 78} This leaves a choice of either a eutectic mixture of individual R and S crystals or a solid solution capable of containing both enantiomers in all proportions. If the latter is true, then the solid solution must

be close to ideal since the d spacings remain unchanged as a function of composition. In a nonideal solution one would expect a molar volume change (and hence a change in d spacings) as the composition is varied.

The choice between these two alternatives was easily made by means of a rather fortuitous result. One batch of racemic 1,1'-binaphthyl happened to crystallize from acetone over a few days in especially large crystals (2-4 mm in diameter) which were shown by infrared analysis to be the high-melting form. We were therefore given the opportunity of hand-picking the well-formed crystals for polarimetric analysis.^k If the high-melting form is a eutectic mixture of individual R and S crystals, then each single crystal should possess a high optical rotation in either direction. If it is an ideal solid solution, then the lattice can accommodate either antipode with equal ease. The single crystals would then grow by selecting randomly either R or S molecules from a racemic solution, and would therefore possess, most probably, a rotation of zero.

The crystals were examined under the polarizing microscope. No hemihedral faces were distinguishable. Although such enantiomorphous faces are always present in eutectic mixtures of enantiomers, they are not always sufficiently well developed to be easily observed.⁴⁶ However, the single crystals were readily recognized under the microscope

^k The picking apart of single crystals, the oldest method of resolving racemic materials,⁴⁶ has never been widely used and remains somewhat of a novelty. However this procedure, which is not synthetically useful because of the small quantities involved, can give valuable information about the nature of the racemic modification, or even the very existence of optical activity in a given material. Very recently Wynberg⁷⁹ has used this method to resolve several hetero-helicenes.

by looking for total extinction on rotation of the microscope stage between crossed polars. A sketch of the habit of these crystals is shown in Figure 10. The crystal would extinguish when viewed in any position other than normal to the c and d faces. Such a failure to extinguish will arise when an optically active crystal is being viewed along an optic axis,⁸⁰ a preliminary indication that each crystal being examined contains molecules of only one enantiomer.

Ten well formed single crystals were carefully separated from the mixture, dissolved in benzene, and analyzed for activity. The results (Table VI) show that each crystal was highly resolved (nine out of ten

Table VI
Specific Rotations of Single Crystals Obtained from the Recrystallization
of Racemic 1,1'-Binaphthyl

Crystal Number	Weight, mg	[α], degrees
1	2.45	+222
2	6.20	+208
3	6.45	+203
4	6.25	+207
5	11.10	-199
6	11.30	+212
7	7.85	-164
8	8.55	-204
9	5.30	+222
10	9.55	+197

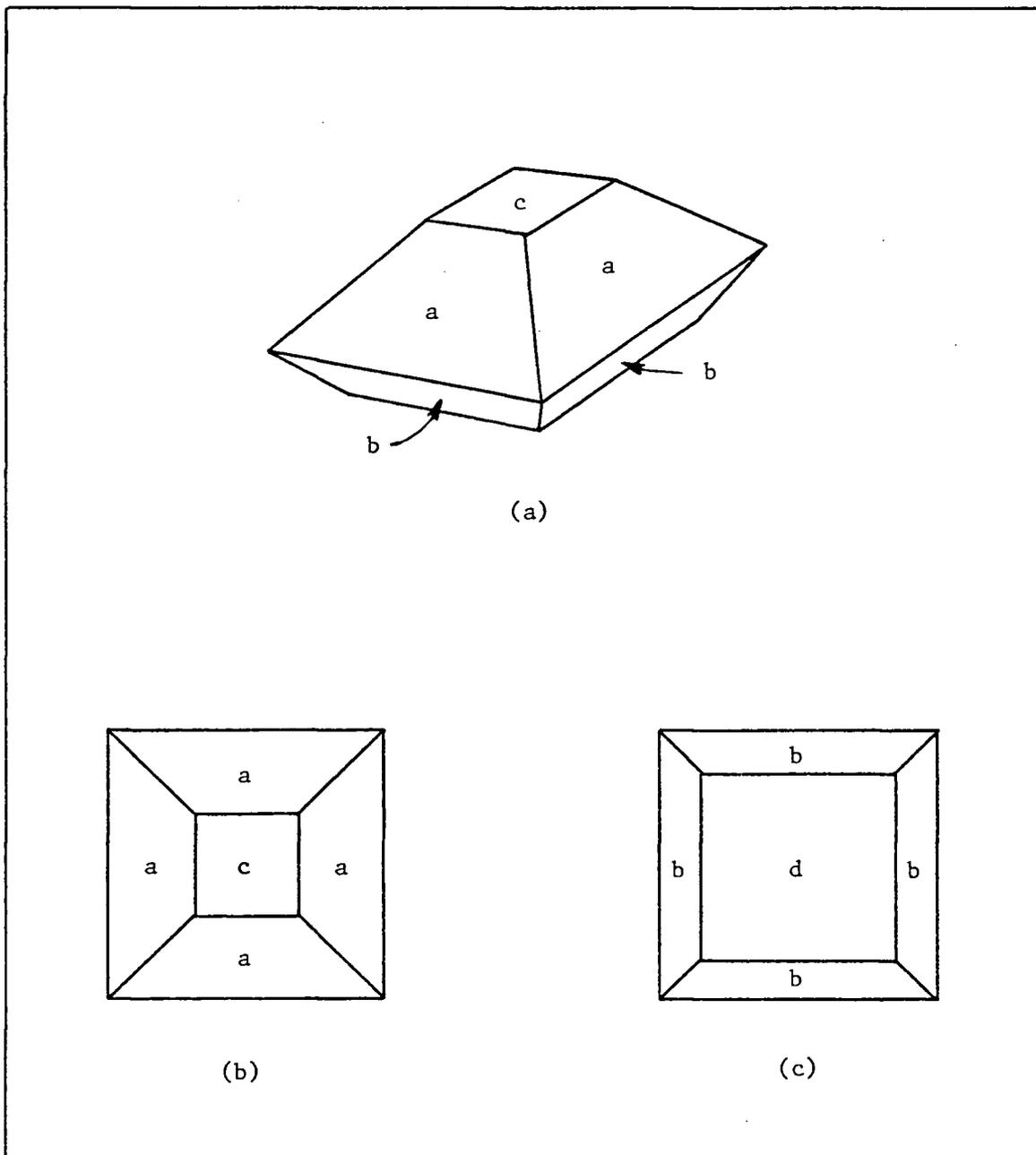


Figure 10. Sketch of the habit of a single crystal of pure R- or S-1,1'-binaphthyl, showing those faces which were apparent under the microscope. (a) View of a, b, and c faces. (b) View normal to c face. (c) View normal to d face.

were at least 80% resolved), and that both R and S crystals were present in the mixture. The high-melting form is therefore a eutectic mixture of individual R and S crystals.

In this thesis, the words "eutectic form" will be synonymous with "high-melting form," and will apply to mixtures of R and S crystals in any ratio, from 100% R, through the racemic composition (where an equimolar mixture of R and S crystals exist), to 100% S. The eutectic form is not a single solid phase like the racemate (low-melting form), but consists instead of two solid phases, an R phase and an S phase. The high-melting form is not considered a polymorph^{81a} of the low-melting form.

Although the nature of both the low- and high-melting modifications of crystalline 1,1'-binaphthyl are now known, the phase diagram cannot yet be constructed. Some information as to the temperature ranges over which each form is stable, must be obtained. This problem and its connection to the solid-state resolution will be considered next.

3.3.2 Relative Stability of the Phases

The simplest way to determine which of two phases lies lowest in free energy at a given temperature and composition (i.e., at a given point on the phase diagram) is to observe the conversion of one to another at the point in question. With fast transformations (such as melting) this observation is easily made. If the phase changes are slow the problem becomes more difficult. In the course of this work, several approaches were necessary in determining the relative stability

of all 1,1'-binaphthyl phases.

3.3.2.1 Melting Point Observations

The original distinction between the two crystalline modifications of 1,1'-binaphthyl was based on melting points.⁷³ We confirmed that the low-melting form (a racemate) melts at 144-145°, and that the high-melting form (a eutectic mixture) melts at 157-158°. In fact, all samples of high-melting form, from $[\alpha] = 0$ to $\pm 245^\circ$, melted at 157-158°. This observation at first appears to contradict our earlier findings, since eutectic mixtures of enantiomers characteristically melt lower at the racemic than at the resolved composition. However, since a mechanism exists for the interconversion of enantiomers, the system R- and S-1,1'-binaphthyl is a pseudobinary system (Section 2.3.2, p 32). If racemization in the melt is rapid, the melting points may be observed to occur far below the ideal values.

The presence of facile racemization in the melt was easily verified. A 20 mg sample of 1,1'-binaphthyl ($[\alpha] = +234^\circ$) was sealed in an ampule and immersed in a bath thermostatted at 160.3°. In three minutes the sample attained this temperature and completely melted, and after a total of five minutes it was quenched to room temperature. Analysis gave $[\alpha] = 0.0 \pm 0.5^\circ$. If solution rates of racemization of 1,1'-binaphthyl⁶⁴⁻⁶⁶ are extrapolated to this temperature, the half-life is less than 0.5 sec. Racemization is virtually instantaneous, and a relatively slow rate of heating (1 deg min⁻¹ in a capillary melting point apparatus, or even 40 deg min⁻¹ with a differential scanning calorimeter, as mentioned in the following section)

would account for the observation of a melting point which is independent of composition. The ideal melting point of pure R- or S-1,1'-binaphthyl is therefore impossible to determine.¹

1,1'-Binaphthyl which has been melted above 158° supercools to a great extent. Some melted samples can be held at 125° indefinitely without crystallization. However, the addition of seed crystals of high-melting form to the melt just below 158° readily causes crystallization. Similar observations of the metastability of the 1,1'-binaphthyl melt have been made by Binns and Squire,⁸² who reported that samples could be cooled as low as 120° without crystallization.

Samples of low-melting form containing very little of the eutectic modification melted essentially completely at 144-145°. However, if the samples contained larger quantities of the higher melting eutectic, the latter readily crystallized from the melt of the former in the temperature range 145-158°. If crystallization of this form was especially efficient, the sample did not appear to melt at all at 145°. In such cases, some melting could be observed if the sample was rapidly immersed in a temperature bath between 145-158°.

From these observed transitions (eutectic form → melt at 157-158°, racemate → melt → eutectic form from 145° to 158°, and melt → eutectic form below 158°), some ordering of the free energy surfaces associated with each phase can be deduced. The two possible free energy situations

¹ The behaviour of 1,1'-binaphthyl on melting emphasizes the dangers in using melting point as a means of deducing phase systems between optical isomers. Although commonly used,⁴⁶ the melting point diagram can lead to erroneous conclusions if the enantiomers are optically unstable.

are illustrated schematically in Figure 11 (a) and (b). The free energy-temperature diagrams are taken at the racemic composition and at constant pressure (atmospheric). These curves resemble those for the two ways in which the phases of a single component exhibiting dimorphism can be related: the monotropic (Figure 11 (a)) and the enantiotropic (Figure 11 (b)) relationship.^{49b,51,81b} In the first, the low-melting form (L) is unstable relative to the high-melting form (H) at all temperatures below 158°. At 145°, L intersects the melt surface (M) and melts metastably. Between 145° and 158°, any high-melting form in the sample causes crystallization of this melt and a lowering of the free energy of the system. At 158°, the high-melting form can exist in stable equilibrium with the melt. In the second relationship (Figure 11 (b)), the low-melting form is stable below a transition temperature (τ), but exhibits the same melting behaviour as in the monotropic case. The choice between the two possibilities lies in establishing the presence or absence of the solid-solid transition point τ .

We now have enough information to postulate a mechanism for the resolution reaction. At 150°, the increase in optical rotation evidently occurs because the racemate phase melts, leaving crystals of R- and S-1,1'-binaphthyl (eutectic form) behind to act as seeds for the ensuing melt \rightarrow eutectic form transformation. If the eutectic form in the original sample consists only of S crystals, then the preferential crystallization only of S-1,1'-binaphthyl can occur, the supply of S molecules being maintained by the rapid enantiomer interconversion in the melt phase. Conversion of the entire sample to pure S-1,1'-binaphthyl is therefore possible, provided the unwanted R crystals have been

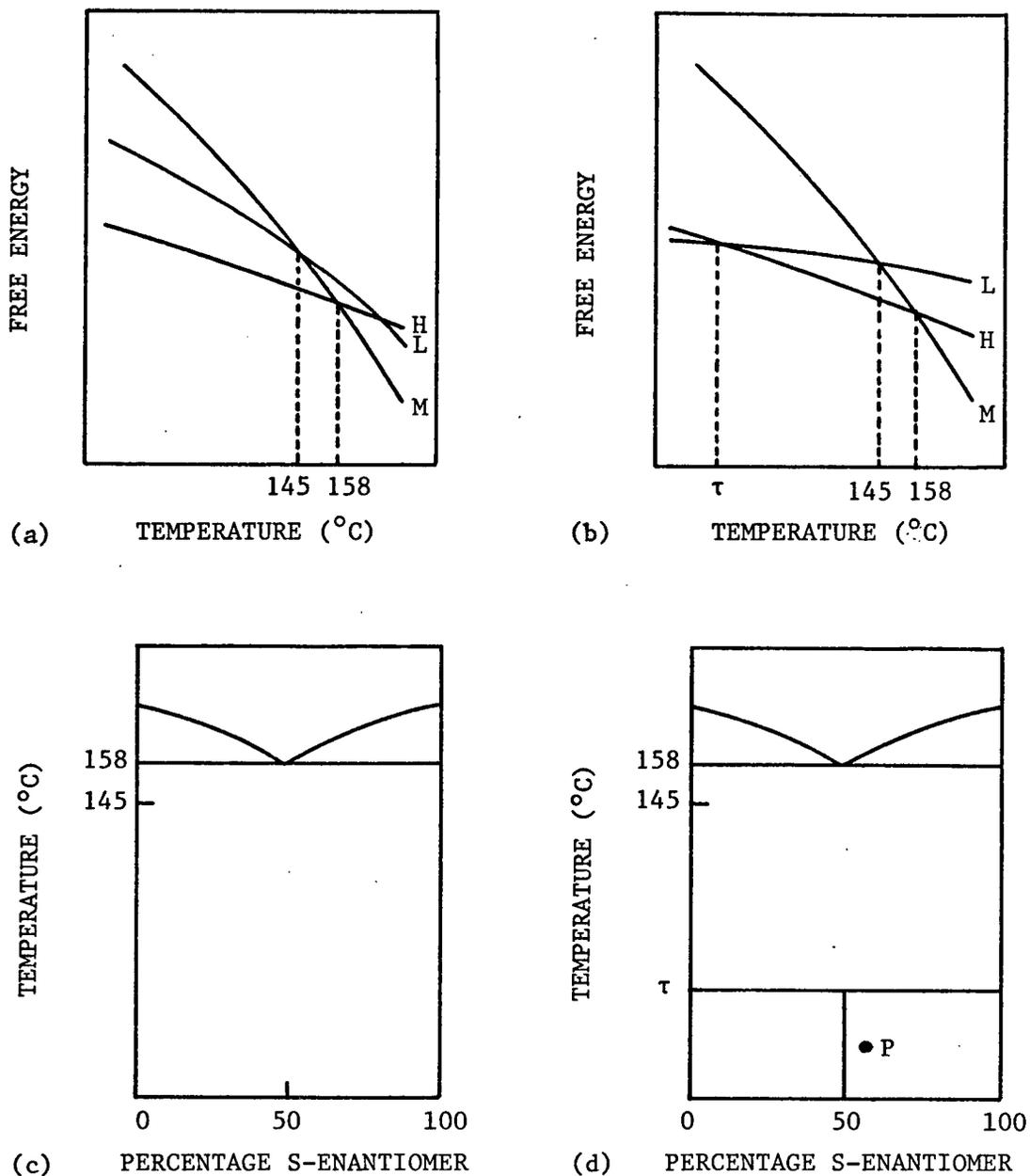


Figure 11. Schematic free energy-temperature plots for racemic 1,1'-binaphthyl, showing low-melting form (L), high-melting form (H) and melt (M) surfaces. (a) Monotropic relationship. (b) Enantiotropic relationship. (c) Phase diagram which would result from the monotropic relationship. (d) Phase diagram which would result from the enantiotropic relationship.

eliminated.

From studying the possible phase diagrams arising from the monotropic and enantiotropic relationships (Figure 11 (c) and (d)), an important conclusion can be drawn. If the system is enantiotropic, then a partially active sample of 1,1'-binaphthyl held at point p contains only S crystals and racemate crystals when in its most stable state. Such a sample, on heating to 150°, should therefore totally resolve to S-1,1'-binaphthyl because of the absence of R crystals. Thermodynamics would therefore be operating so as to favour the production of a highly stereospecific sample of solid 1,1'-binaphthyl. It is very desirable, then, to know which phase diagram describes the R- and S-1,1'-binaphthyl system.

3.3.2.2 Differential Scanning Calorimetry - Qualitative

The differential scanning calorimeter is very helpful in determining phase diagrams (Section 2.3.1, p 27). In the course of our studies, many hundreds of samples of 1,1'-binaphthyl were run on the d.s.c. In none of the samples was any sign of a solid-solid transition apparent. The only peaks occurred from 145° to 158°. A typical d.s.c. trace of a sample containing both the low-melting (racemate) and high-melting (eutectic) forms is shown in Figure 12 as a function of programming (heating) rate. Two endotherms and an exotherm are discernible. The first endotherm, at 144-145°, corresponds to the metastable melting of the racemate. This is followed immediately by the exothermic crystallization of the eutectic form from the melt, then finally by the (endothermic) melting of the eutectic form. The final endotherm there-

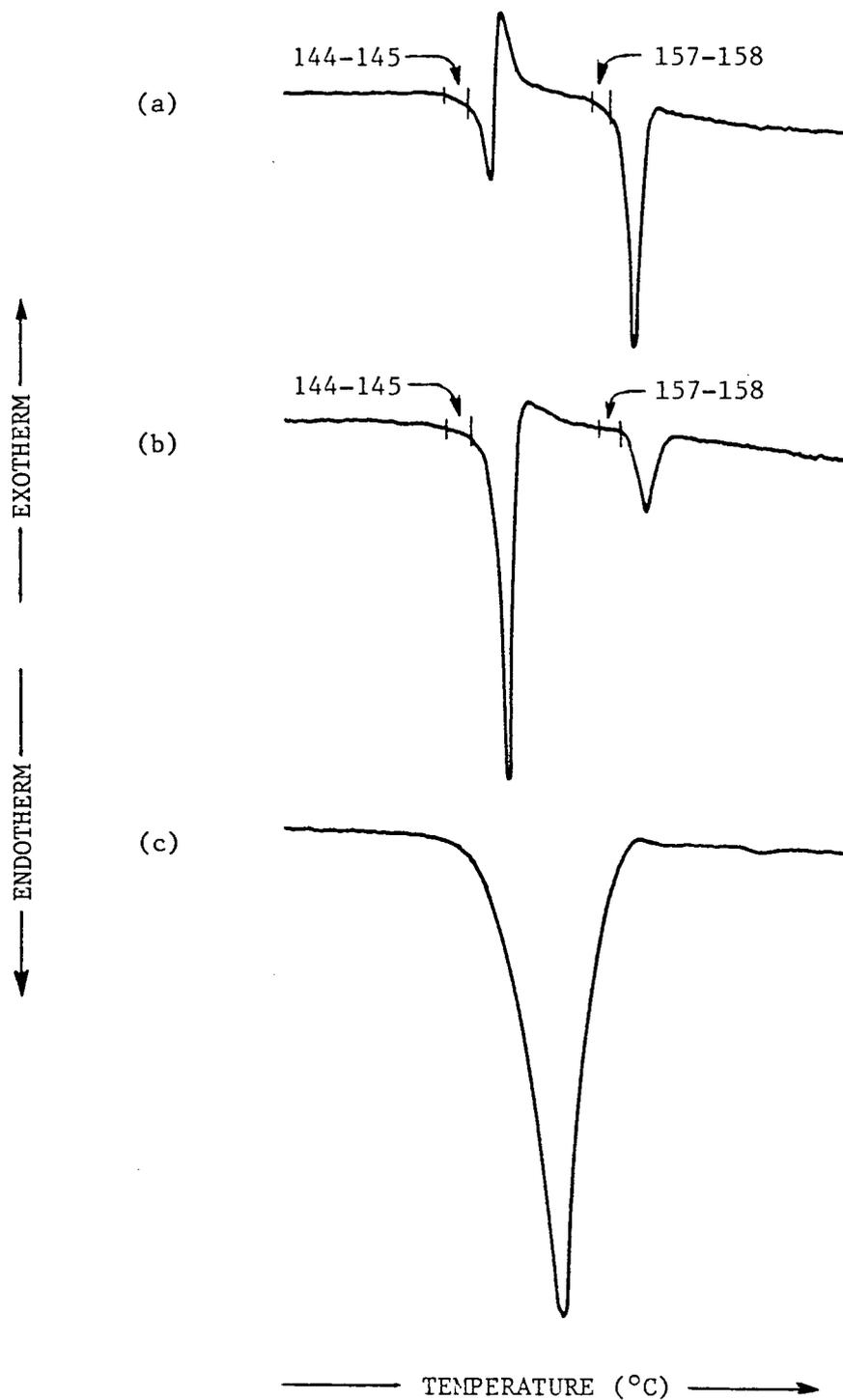


Figure 12. Differential scanning calorimeter traces for racemic 1,1'-binaphthyl, as a function of programming rate. (a) 2.5 deg min^{-1} (b) 10 deg min^{-1} (c) 40 deg min^{-1}

fore comprises both the eutectic form originally present in the sample plus that which crystallized from the melt of the racemate. At faster programming rates, the diminished size of the final endotherm and of the exotherm mean that the original sample did not contain much eutectic form. Rather, most of it crystallized from the melt at slower heating rates.

Pure high-melting form (obtained by holding any sample of 1,1'-binaphthyl at 150°) shows a single endotherm at 157-158° regardless of the specific rotation of the sample. Even at 40 deg min⁻¹, the temperature of the endotherm (apparently slightly higher because of the thermal resistance of the instrument) is the same whether the sample is resolved or racemic. As just explained (Section 3.3.2.1), constancy of melting point with composition will occur when extremely rapid enantiomer interconversion takes place on melting.

Since it is impossible to crystallize the high-melting form from the melt at 150° without the use of seed crystals, the appearance of the higher temperature endotherm on d.s.c. analysis of 1,1'-binaphthyl implies that this form must have been present in the original sample in at least trace ("seed") quantities. Thermal analyses of dozens of different samples of 1,1'-binaphthyl prepared in various ways showed that it was impossible to produce workable quantities of low-melting form containing absolutely no seed crystals of the high-melting form. All showed endotherms at 157-158°. Some samples were especially low in this eutectic content, since no high-melting endotherm was observed at the usual heating rate of 10 deg min⁻¹. However, on reducing the rate to 2.5 deg min⁻¹, some eutectic form crystallized then melted, indicating

traces of this form in the sample. This method is therefore a sensitive check of the "phase purity" of low-melting samples.

One single procedure did, however, produce absolutely pure low-melting form in small quantities. When pure 1,1'-binaphthyl, regardless of its phase content or activity, was melted above 160° on the d.s.c., then program cooled (at rates up to 20 deg min⁻¹) to 50-60°, the sample solidified. On reheating at any programming rate, only the racemate endotherm was observed; no eutectic form crystallized from the melt above 145°. In contrast, if the same sample is melted above 160° and cooled very quickly by removing the sample planchette and placing it on a metal surface at room temperature, a glass forms; if the sample is replaced in the holder then reheated, it solidifies at about 90-100°, then melts at 157-158°, with no indication of any low-melting form. This micro (<5 mg) method of preparing the pure high- and low-melting forms is surprisingly reproducible - the same sample can be converted back and forth indefinitely to either form, simply by varying the rate of cooling.

What do these qualitative d.s.c. observations tell us about the relative stability of the two crystalline modifications? First of all, they verify the ordering of the free energies of racemic 1,1'-binaphthyl in the region of the melting points (145° to 158°). Secondly, the manner in which the low- and high-melting form can be reproducibly obtained with the d.s.c. is revealing. In the experience of McCrone,^{81c} if two polymorphs are obtained by cooling the melt in different ways, the least stable form is that which crystallizes from the most highly supercooled melt. Melts can be highly supercooled when a small amount is cooled very

rapidly, like the way in which the high-melting form was produced in the d.s.c. planchette. The suggestion is therefore that at lower temperatures the low-melting form is the more stable modification.

These observations with a supercooled melt should also obtain with a supersaturated solution.^{81c} That is, the more highly supersaturated solution should yield the less stable of the two forms. Accordingly, we prepared filtered solutions of racemic 1,1'-binaphthyl in ether, acetone, and benzene. These were allowed to evaporate slowly at room temperature over several days. In each case the resulting crystals were racemate form with very few seeds of eutectic form, as revealed by d.s.c. analysis. Similarly prepared solutions were evaporated quickly (in less than five minutes) in a stream of dry air at room temperature. The eutectic form was obtained in high phase purity (X-ray analysis). If it is true that the more supersaturated conditions produce the less stable form, then again the implication is that the racemate is stable at room temperature.

Following this empirical principle to its limit, we decided to search for any other crystal modifications (less stable than the low- and high-melting forms) by creating an extremely supercooled melt. To this end, some racemic 1,1'-binaphthyl was packed in an X-ray powder capillary then melted in a 175° bath. The capillary was then immediately immersed into a bath of liquid nitrogen. A glassy substance formed in the tube. The capillary was then mounted in the powder camera and exposed to X-rays for 20 h. Within four hours the sample solidified. The diffraction pattern showed lines due only to the racemate and the eutectic form, and no other crystal modification.

3.3.2.3 Differential Scanning Calorimetry - Quantitative

Although the above observations suggest an enantiotropic relationship, a more quantitative approach would be very helpful. Specifically, if the actual free energy difference between the racemate and the eutectic forms could be calculated as a function of temperature at constant pressure and composition (the racemic composition), then the stable ranges of each could be determined. In other organic solids, free energy calculations have been used for just this purpose.^{83,84}

Sufficient information in the melting region of 1,1'-binaphthyl is available to allow calculation of the free energy difference between the two crystal modifications at 150°C (423°K). This can be seen from the free energy plots (Figure 11 (a) and (b)) and the schematic enthalpy and entropy plots of Figure 13. The enthalpy difference in going from the low-melting (racemate) form to the melt (L→M) can be calculated from the area of the d.s.c. endotherm at 145°C (418°K). Similarly, the enthalpy change high-melting (eutectic) form → melt (H→M) at 158°C (431°K) can be determined. Since the free energy change at these two points is zero, the entropy change on melting can be calculated for both forms:

$$\Delta G_{418}^{L \rightarrow M} = 0 = \Delta H_{418}^{L \rightarrow M} - (418)\Delta S_{418}^{L \rightarrow M}$$

$$\Delta G_{431}^{H \rightarrow M} = 0 = \Delta H_{431}^{H \rightarrow M} - (431)\Delta S_{431}^{H \rightarrow M}$$

$$[10] \quad \Delta S_{418}^{L \rightarrow M} = \frac{\Delta H_{418}^{L \rightarrow M}}{(418)} \quad \text{and} \quad \Delta S_{431}^{H \rightarrow M} = \frac{\Delta H_{431}^{H \rightarrow M}}{(431)}$$

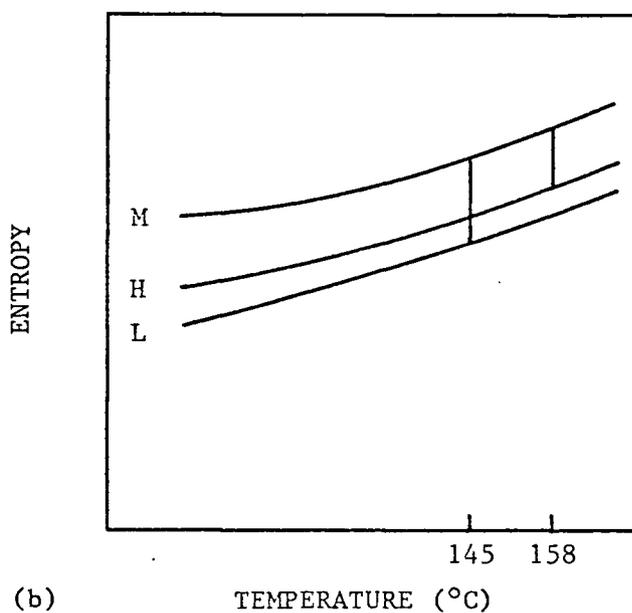
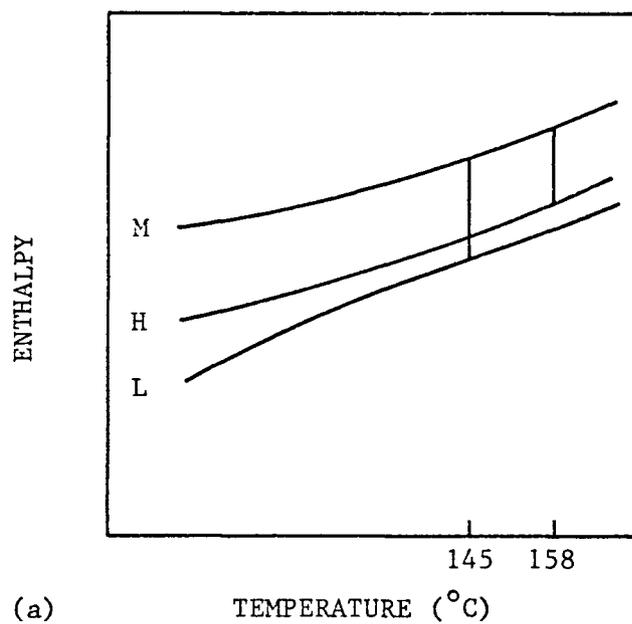


Figure 13. Schematic enthalpy- and entropy-temperature plots for racemic 1,1'-binaphthyl. (a) Ordering of low-melting form (L), high-melting form (H) and melt (M) enthalpies. (b) Ordering of entropies of the same phases.

where the subscript refers to the absolute temperature of the transition. Since 150°C is close to the melting points of both forms (145°C and 158°C), we may assume to a good approximation that the enthalpy and entropy changes on melting are identical to the corresponding changes at 150°C (423°K).⁶¹ That is,

$$\begin{aligned}
 [11] \quad \Delta H_{418}^{L \rightarrow M} &= \Delta H_{423}^{L \rightarrow M} & \Delta H_{431}^{H \rightarrow M} &= \Delta H_{423}^{H \rightarrow M} \\
 \Delta S_{418}^{L \rightarrow M} &= \Delta S_{423}^{L \rightarrow M} & \Delta S_{431}^{H \rightarrow M} &= \Delta S_{423}^{H \rightarrow M}
 \end{aligned}$$

and

This approximation allows us to calculate the enthalpy, entropy, and free energy difference between the two crystalline forms (L and H) at 150°C ($\Delta H_{423}^{L \rightarrow H}$, $\Delta S_{423}^{L \rightarrow H}$ and $\Delta G_{423}^{L \rightarrow H}$, respectively).

$$[12] \quad \Delta H_{423}^{L \rightarrow H} = \Delta H_{423}^{L \rightarrow M} - \Delta H_{423}^{H \rightarrow M} = \Delta H_{418}^{L \rightarrow M} - \Delta H_{431}^{H \rightarrow M}$$

$$[13] \quad \Delta S_{423}^{L \rightarrow H} = \Delta S_{423}^{L \rightarrow M} - \Delta S_{423}^{H \rightarrow M} = \Delta S_{418}^{L \rightarrow M} - \Delta S_{431}^{H \rightarrow M}$$

$$[14] \quad \Delta G_{423}^{L \rightarrow H} = \Delta H_{423}^{L \rightarrow H} - (423) \Delta S_{423}^{L \rightarrow H}$$

Before proceeding to show how this free energy difference can be determined as a function of temperature, we shall present our results thus far. The enthalpy of melting for the racemate ($\Delta H_{418}^{L \rightarrow M}$) was determined with a sample which contained negligible eutectic form and did not crystallize any eutectic form from the melt above 145°C (418°K). The endotherm was a single, sharp peak, from which an enthalpy of 7.29 ± 0.15 kcal mole⁻¹ (28.6 ± 0.6 cal g⁻¹) was obtained. The entropy change, calculated from Equation 10, is $\Delta S_{418}^{L \rightarrow M} = 17.48 \pm 0.40$ cal deg⁻¹ mole⁻¹.

Endotherms corresponding to the melting of the eutectic form were similarly used to calculate $\Delta H_{431}^{H \rightarrow M}$. However, the eutectic is capable of having any specific rotation, depending on the relative amounts of R and S crystals in the mixture. Therefore, enthalpies of fusion were determined for several samples of eutectic form possessing different activities (Table VII). Several determinations were made for each sample,

TABLE VII

Enthalpy of Fusion of the High-Melting Form of 1,1'-Binaphthyl at Various Specific Rotations

[α], degrees	$\Delta H_{431}^{H \rightarrow M}$, kcal mole ⁻¹ , multiple analyses	$\Delta H_{431}^{H \rightarrow M}$, kcal mole ⁻¹ , mean value
-245	5.11, 4.70	4.91
-205	5.12, 5.28, 5.13, 5.36	5.22
-8	5.68, 5.61, 5.72, 5.65	5.67
+137	5.85, 5.43, 5.85, 5.43	5.64
+154	5.72, 5.68	5.70
+223	4.51, 4.95, 4.68, 5.07	4.80
+238	4.39, 4.60	4.50

because all gave endotherms with a slight leading edge, which can produce errors when the peaks are integrated.⁴⁷ Comparing the mean values, the samples having high rotations possess somewhat lower values of $\Delta H_{431}^{H \rightarrow M}$. Since the final state in melting eutectic form of any activity is the

racemic melt, the lower enthalpies could reflect a difference in enthalpy between resolved and racemic eutectic form. However the differences are perhaps too close to the scatter in individual analyses to be considered seriously. Moreover, our goal is to determine relative free energies of the racemic system. For this purpose the enthalpy of fusion of the $[\alpha] = -8^\circ$ sample (5.67 ± 0.08 kcal mole⁻¹ or 22.3 ± 0.3 cal g⁻¹) will be used. The corresponding entropy change is $\Delta S_{431}^{H \rightarrow M} = 13.15 \pm 0.22$ cal deg⁻¹ mole⁻¹.

The magnitudes of the determined enthalpy and entropy of fusion for both the low- and high-melting forms justifies the ordering of the schematic enthalpy and entropy surfaces in Figure 13.

Application of Equations 12, 13 and 14 gives the enthalpy, entropy and free energy differences between the racemate and the eutectic forms at 150°C (423°K):

$$\Delta H_{423}^{L \rightarrow H} = (7.29 - 5.67) \text{ kcal mole}^{-1} = 1.62 \pm 0.23 \text{ kcal mole}^{-1}$$

$$\Delta S_{423}^{L \rightarrow H} = (17.48 - 13.15) \text{ cal deg}^{-1} \text{ mole}^{-1} = 4.33 \pm 0.62 \text{ cal deg}^{-1} \text{ mole}^{-1}$$

$$\Delta G_{423}^{L \rightarrow H} = [1620 - (423)(4.33)] \text{ cal mole}^{-1} = -212 \pm 490 \text{ cal mole}^{-1}$$

The rather large error limits in these values is disappointing. Although the enthalpies and entropies of fusion for the racemate and eutectic forms have been measured to less than 2.3% uncertainty, the differences $\Delta H_{423}^{L \rightarrow H}$ and $\Delta S_{423}^{L \rightarrow H}$ are relatively small and involve subtracting two measured values, resulting in a 14% relative uncertainty. Finally, performing a second subtraction to obtain $\Delta G_{423}^{L \rightarrow H}$ produces a very large

uncertainty. Even the algebraic sign of the free energy difference, the important criterion for relative stability, is in some doubt. The numerical result $\Delta G_{423}^{L \rightarrow H} = -212 \text{ cal mole}^{-1}$ represents the most probable value of the free energy difference at 150°C. The fact that this difference is most probably negative is in accord with our experimental results - the eutectic form is indeed produced from the melt of the racemate at 150°C (see Figure 11 (a) and (b), p 67).

Any further discussion of how the free energy difference might change with temperature therefore involves most probable values. There is still some advantage in proceeding with such a treatment, with the hope that it may support the existence of a solid-solid transition temperature τ , even if a precise value is not obtainable. Because of the rather lengthy development necessary, this treatment is presented in Appendix B, p 184.

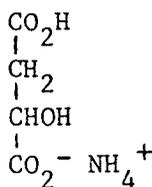
Let us now summarize the evidence for the enantiotropic ordering of racemic modifications. First of all, slow and rapid cooling of the melt on the d.s.c. gives racemate and eutectic form, respectively. Slow and rapid evaporation of solutions at room temperature give the same results. These observations are consistent with the racemate being the more stable form at room temperature. Since the less stable of two forms "rarely, if ever" can be produced above the temperature at which both have equal free energies,^{81c} the fact that both can be obtained at all by recrystallization at room temperature implies that τ is above room temperature. Anticipating a result presented in Section 3.5.1 (p 112), we have found that the lowest temperature at which the racemate \rightarrow eutectic form transformation can be observed is 76°C,

so that τ must be lower than this temperature. The treatment in Appendix B supports the enantiotropic relationship, with a most probable transition temperature of 86°C.

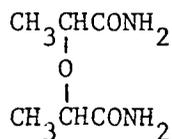
These independent observations together are consistent with the system R- and S-1,1'-binaphthyl possessing an enantiotropic phase relationship at the racemic composition, and a phase diagram like that in Figure 11 (d), p 67, with the transition temperature τ between 25 and 76°C. Because the higher temperature limit is closer to the calculated most probable transition temperature, the value of τ will be taken as ca. 70°C for the remainder of this thesis.

3.3.3 The Stable and Metastable Phase Diagram

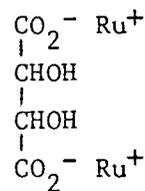
The phase diagram for the R- and S-1,1'-binaphthyl system is redrawn in Figure 14 (a). The solid lines represent phase boundaries reflecting the lowest free energy surfaces in a temperature-composition-free energy plot (Section 2.3.2, p 32). This type of phase diagram (two racemic modifications, where a racemate is the low temperature form and a eutectic mixture is the high temperature form) has also been observed with (+)-



34



35



36

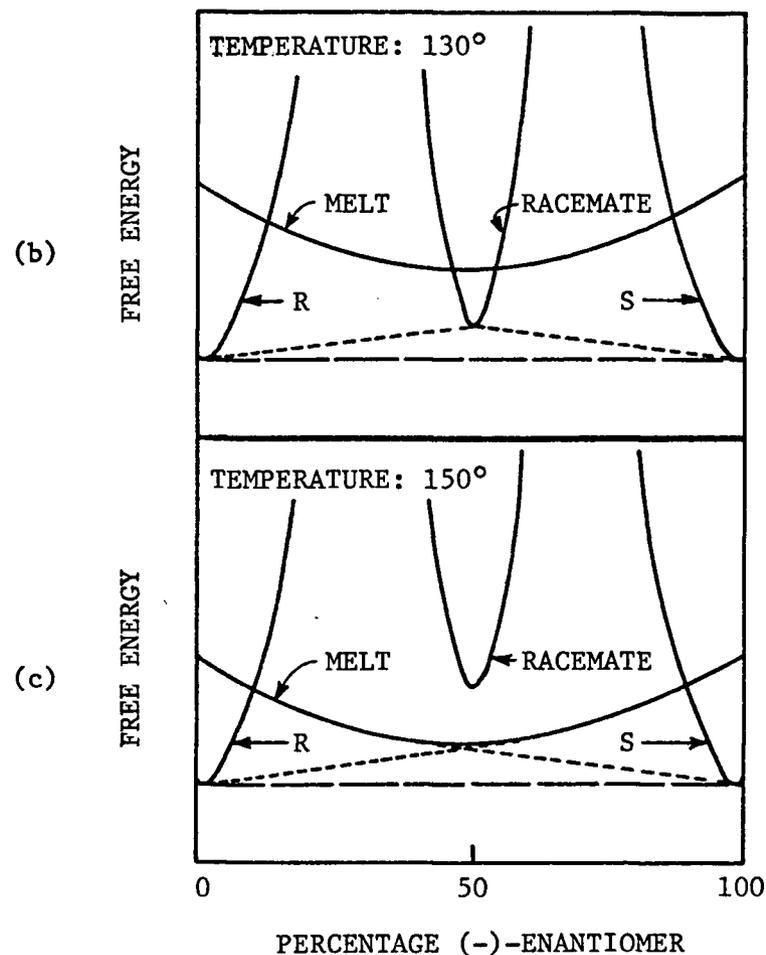
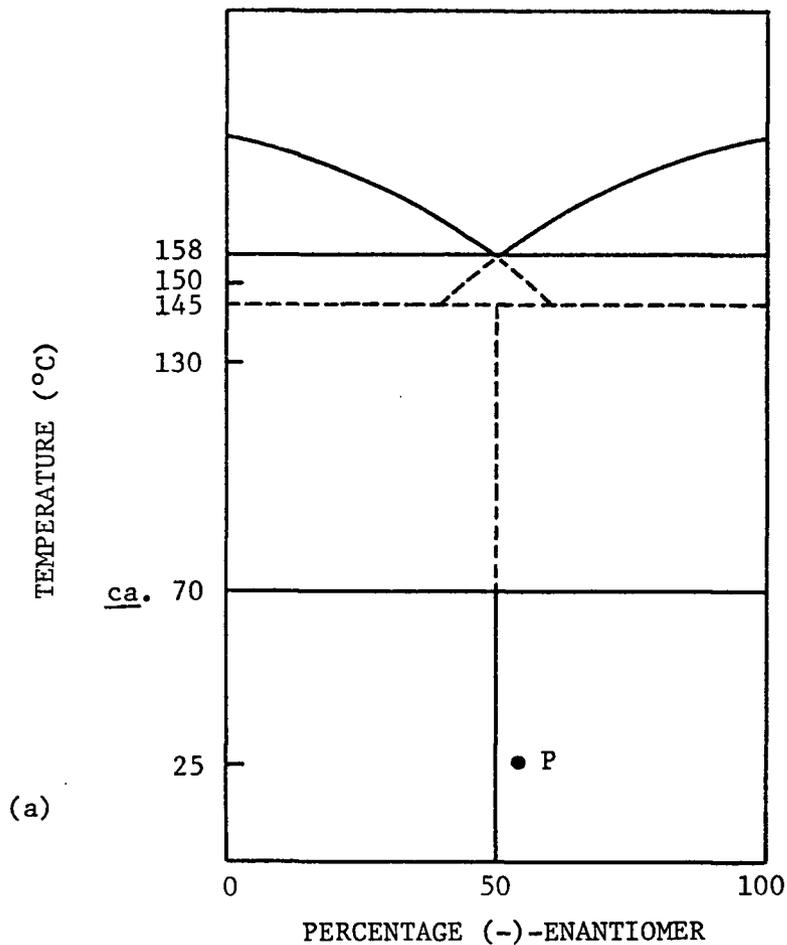


Figure 14. (a) Phase diagram for the R- and S-1,1'-binaphthyl system, showing metastable extensions (dotted lines) of the phase boundaries. (b) Schematic free energy-composition plot at 130°, showing the lowest (dashed line) and next-lowest (dotted lines) free energy surfaces. (c) As for (b), but at 150°.

and (-)-ammonium hydrogen malate (34), where $\tau = 73^\circ$; ⁸⁵ with (+)- and (-)-dilactyldiamide (35), where $\tau = 35^\circ$; ⁸⁵ with (+)- and (-)-rubidium tartrate (36), where $\tau = 40^\circ$; ^{45d} and with the complex salt (+)- and (-)- $[\text{Co}(\text{C}_2\text{O}_4)_3]\text{K}_3 \cdot 3.5\text{H}_2\text{O}$, where $\tau = 13^\circ$. ⁸⁵

The phase diagram representing the lowest free energy surfaces will not show any structure for the melting of the 1,1'-binaphthyl racemate at 145° , since this transformation is metastable and occurs between phases which are at higher free energies at this temperature. However the transformation is very real and for this reason we have deduced the metastable phase boundaries and superimposed them on Figure 14 (a) (dotted lines). The areas enclosed by the dotted lines have no significance in the phase rule sense; they merely represent metastable extrapolations of the stable areas, and must be considered individually. The origin of the dotted lines can be seen in the schematic free energy-composition plot at constant pressure and at 130° (Figure 14 (b)) and at 150° (Figure 14 (c)). The most stable free energy arrangement at both of these temperatures is shown by the dashed line, and is seen to be a eutectic mixture of R and S crystals, as determined experimentally. The next most stable arrangement is shown by the dotted lines in Figure 14 (b) and (c). At 130° , these connect solid R with racemate on one side of the diagram, and solid S with racemate on the other, in the same manner as they do stably below ca. 70° . At 150° , similar dotted lines connect R and S crystals individually to the melt phase, an arrangement which is lowest in free energy above 158° . In going to higher temperatures, the racemic melt decreases in free energy

relative to the racemate and the eutectic mixture, becoming lower than the racemate at 145° and lower than the eutectic mixture at 158° (see also Figure 11 (b), p 67).

If a partially resolved sample of S-1,1'-binaphthyl attains its most stable state at 25° (point p, Figure 14 (a)), it will consist only of S crystals and racemate crystals. When the sample is heated to 150° (or, for that matter, any temperature between 145° and 158°), the racemate will melt in the presence of the more stable S crystals. If these crystals exercise complete control over the ensuing crystallization, then the entire sample will become S-(+)-1,1'-binaphthyl in a drive toward lower free energy. Preparation of the correct initial material (discussed in Section 3.4, which follows) should therefore result in complete resolution in a single step.

Likewise, between ca. 70° and 145°, a direct racemate → eutectic transformation would lower the free energy of the system. Preliminary observations at 120° (Table III, p 51) indicate that even without the intermediacy of the melt, enantiomer interconversion is possible, permitting a resolution of 1,1'-binaphthyl completely in the solid state.^m Our extensive kinetic investigations in this temperature range are reported in Section 3.5.

^m We refer to this general phenomenon as a solid-state resolution. At all temperatures, from 70° to 158°, it is a resolution by the solid state - that is, the resolving "agent" is the discriminating surface of the growing crystals of pure enantiomer. Below 145°, the resolution is occurring totally in the solid state, by means of a solid-solid phase transformation.

3.4 Perfection of the Solid-State Resolution

Our initial attempts to resolve neat, polycrystalline 1,1'-binaphthyl (Section 3.2, p 49), although successful, suffered from a lack of reproducibility. The best method we devised was a cycling procedure, which eventually achieved a high resolution, but did so in an unpredictable fashion. Much of our research effort with the 1,1'-binaphthyl system was directed toward trying to achieve some control over the resolution. The determination of the phase diagram was a major step in understanding what originally seemed a very unusual reaction. Perhaps now we could use this knowledge to prepare reproducibly the elusive batch of solid 1,1'-binaphthyl having originally little or no optical rotation but possessing the ability to resolve totally simply on heating the solid material. Once this is accomplished, such a highly stereospecific solid could be used to study the kinetics of the resolution process, enabling, hopefully, a more detailed mechanistic description.

Our several approaches to the problem of reproducibility are treated in this section. We found this task, as did Wynberg^{79a} with his attempted heterohelicene resolutions, "both exciting and frustrating," and in the end, very rewarding.

3.4.1 The Behaviour of Solid Racemic 1,1'-Binaphthyl

Before the more elaborate schemes are discussed, the behaviour of racemic 1,1'-binaphthyl, isolated directly from the Grignard coupling reaction (Section 3.1.2, p 48) should be established. Initially, racemic 1,1'-binaphthyl was used as a control, and heated alongside partially active samples which increased in rotation at 150°. In this way, it was

discovered that even racemic material could develop optical activity on heating. Of the two batches (A and B) of racemic 1,1'-binaphthyl originally studied (Table III, p 51), one (A) did not resolve at all, but the other (B) gave scattered activities, which were all positive.

Throughout the course of this work, several Grignard preparations were performed when stocks of racemic 1,1'-binaphthyl ran low, and it became rather routine to characterize each batch by heating a few samples at 150° and checking for any resolution. Table VIII compiles the results of samples of the racemic material which were heated for various reasons. A different "batch" is prepared each time a given preparation was recrystallized, so that all material within each batch has the same phase content and average crystal size and perfection. Although some were recrystallized in the presence of racemic 1,1'-binaphthyl seeds, there was no deliberate addition of any active crystals.

Racemic 1,1'-binaphthyl shows some very interesting behaviour on heating. Most of the racemic batches (except A, E, G, and O) developed optical activity when heated at temperatures from 100° to 150°. The fact that this resolution occurs below 145° firmly establishes that the melt is not necessary to the resolution process - the direct phase transformation racemate → eutectic form is sufficient to create optical activity. Although the behaviour of some batches is not well defined because of the few samples heated, others (e.g., B and L) were investigated with many samples and revealed a very surprising tendency to develop optical activity in one direction only. For example, the 37 samples taken from Racemic Batch L are plotted in Figure 15 as a function of time. All samples are positive and widely scattered in optical rotation; no kinetic trends are

Table VIII

The Development of Optical Activity on Heating Polycrystalline, Racemic
1,1'-Binaphthyl

Racemic Batch ^a	Temperature, °C	Time, hours	[α], degrees
C	149.6	1	+25
D	"	1	+65
E	"	1	0
F	"	1	+24, 0 ^b
G	"	1	0
I	"	15.5	-63
"	"	13	-77
J	"	19	-52, -45 ^b
"	"	2	-78, -140 ^b
K	"	16	-87, -129 ^b
"	"	5	-124
"	120	46	-108
"	100	120	-5
L	135	0 to 50	see Figure 15
M	135	15	-8, -9 ^b
N	149.6	1	-22
"	"	5	+3
O	"	2	0, 0 ^b

^a For Racemic Batches A and B, see Table III, p 51.

^b Specific rotations of two individual samples heated for the same length of time at the same temperature.

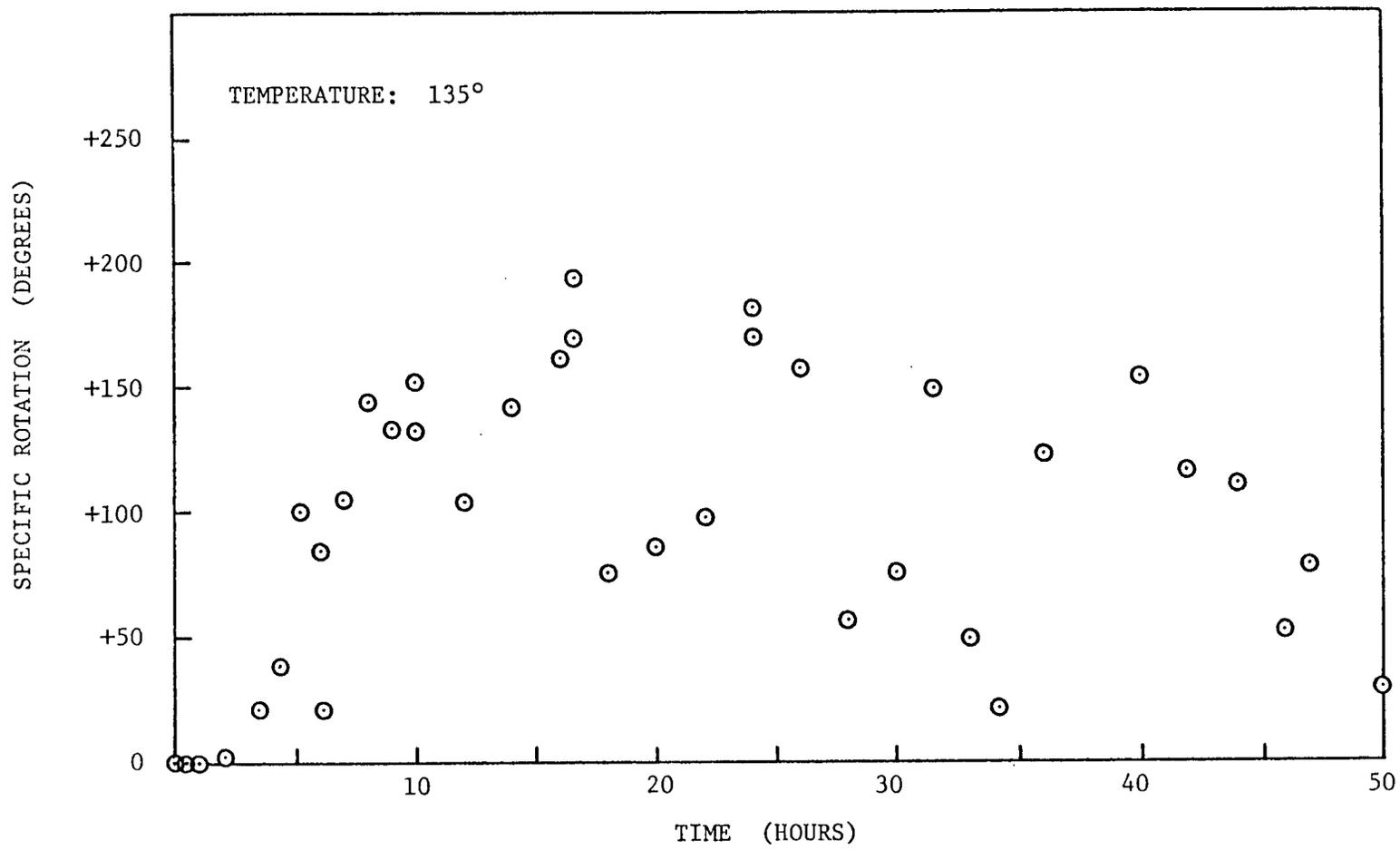


Figure 15. Specific rotation as a function of time for the solid-state resolution of racemic 1,1'-binaphthyl (L Batch) at 135°.

discernible. An equally remarkable result, as already noted, was obtained with Racemic Batch B, where all 11 samples resolved in a positive direction. Some batches (I and J, for example), although investigated less extensively, develop only negative rotations.

1,1'-Binaphthyl prepared from optically inactive reagents seems to possess a built-in stereospecificity. Some dissymmetric influences are present in the batches, which definitely appear racemic when analyzed by polarimetry. As will be proven in Section 3.6, racemic 1,1'-binaphthyl does not possess any foreign dissymmetric impurity which can influence the direction of resolution. Rather, the influences must arise from the 1,1'-binaphthyl system itself, in the form of small, imperceptible excesses of one enantiomer. It is generally recognized⁴⁶ that racemic preparations contain tiny excesses of one enantiomer due to random statistical fluctuations alone. However, our racemic preparations were performed after the first optically active 1,1'-binaphthyl samples were obtained. It is possible therefore that the small excesses could have arisen from resolved 1,1'-binaphthyl dust in our laboratory, which may overshadow any random fluctuations.

Whatever the reason for their existence, these unobservable excesses of one enantiomer can be amplified through the phase interactions in the R- and S-1,1'-binaphthyl system. As revealed by the qualitative d.s.c. results in Section 3.3.2.2 (p 68), every racemic batch contains some eutectic form, even if this is present only in trace quantities. Since any enantiomer excess must be contained in the eutectic form (as a greater number of, say, R than S crystals), then if this form is only a small part of the total sample, the ratio of R to S crystals will be far greater than the ratio of R to S molecules in the

whole sample. On heating, the enantiomer in excess reveals its identity by causing the crystallization of molecules of its own configuration.

The 1,1'-binaphthyl system illustrates a novel method of checking for trace enantiomer excesses, far simpler than the hundreds of recrystallizations on kilogram quantities of "racemic" material which are sometimes necessary to make such excesses observable.⁸⁶

While the manner in which racemic 1,1'-binaphthyl can produce optical activity on heating is very interesting in itself, the specific rotations fall considerably short of complete resolution ($[\alpha] = \pm 245^\circ$). Perhaps changing the method of resolution might make some improvement. The phase changes accompanying the resolution of racemic 1,1'-binaphthyl are racemate \rightarrow melt \rightarrow eutectic form at 150° and racemate \rightarrow eutectic form below 145° . An interesting alternative is racemate \rightarrow solution \rightarrow eutectic form, which is possible when the solid racemic samples are heated in the presence of a saturated solution of 1,1'-binaphthyl in an optically inactive solvent. Such a phase change is called a solution phase transformation,^{81d} and occurs because the more stable of two crystalline modifications is always the less soluble of the two (Figure 16). In the temperature range $70-145^\circ$ the racemate, being the more soluble (and less stable) form, maintains a solution of 1,1'-binaphthyl which is super-saturated with respect to the eutectic form, and the growth of crystals of pure enantiomer can occur from solution. Such a change in growth environment may favourably affect the resolution.

We therefore performed some solution phase transformations in a tube sealed at both ends and divided into two chambers by a fritted disc. The crystals and solvent were located in one end of the tube which was

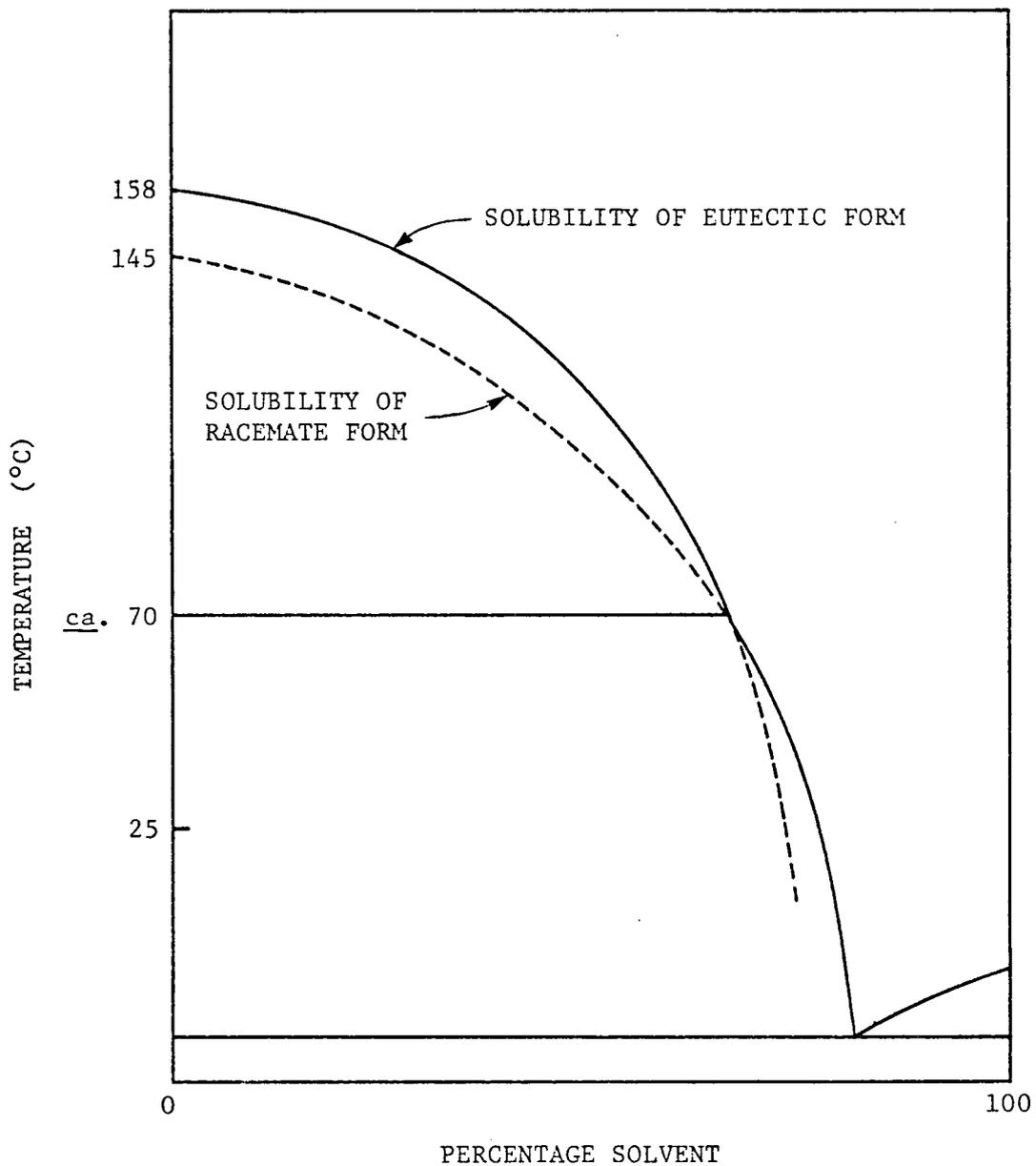


Figure 16. Schematic phase diagram between racemic 1,1'-binaphthyl and a solvent with b.p. > 160°. Dotted lines are metastable extrapolations of phase boundaries, and show the higher solubility of the less stable forms.

totally immersed in a bath held at the temperature of interest. After a period of time the solution could be filtered from the crystals through the sintered glass disc without removing the sample from the temperature bath. The transformed crystals could then be analyzed for optical activity. The results of nine such experiments from 110° to 150° using 2-propanol and ethylene glycol as solvents are listed in Table IX. Racemic Batch I (which, as shown in Table VIII, resolves poorly in the absence of a solvent) was used in the experiments. Although somewhat higher rotations are were observed with 2-propanol at 120°, the best rotations could not be consistently produced. Rather, the activities were scattered, but all were, characteristically, in one direction (negative).

Table IX

The Development of Optical Activity on Heating Polycrystalline, Racemic 1,1'-Binaphthyl^a Under a Solvent

Solvent	Temperature, °C	Time, hours	[α], degrees
Ethylene glycol	110	17	0
" "	130	24	-84
" "	149.6	43	-2.5
2-Propanol	90	15	0
"	120	17	-158
"	"	43	-198
"	"	65	-186
"	"	19	-180
"	"	43	-144

^a All samples were taken from Racemic Batch I.

3.4.2 Physical Addition of Seed Crystals of Active 1,1'-Binaphthyl

It appears that the few crystals of R and/or S-1,1'-binaphthyl which happen to exist in the racemic samples, while efficiently governing the direction of the development of activity, cannot control the magnitude of the rotation. This may occur because these crystals are too few and too widely scattered to be fully effective as seeds. At this point we decided to abandon the racemic system and to introduce mechanically some seed crystals of highly resolved 1,1'-binaphthyl to the polycrystalline material, hoping to "swamp out" the effect of the original seeds and to control the resolution artificially. This physical seeding was done with five batches of racemic 1,1'-binaphthyl, with the results in Table X. Usually, the added seed comprised less than 3% of the total weight of the sample, accounting itself for less than 6° specific rotation. The seed crystals were added in powdered form to the racemic material, contained in a glass ampule. The ampule was then sealed, shaken vigorously for five minutes to distribute the added seeds, and then heated. In two cases (F and G) the resolvability of the racemic material (Table VIII, p 85) was improved. However, rotations were never very high, and with Batch I, seeds of both positive and negative rotations simply decreased the negative activities developed in the unseeded, racemic material. This failure of the physical addition of seeds is probably a reflection of the difficulty in mixing two solids (i.e., seed crystals and racemic material) mechanically.

Perhaps the addition of seed crystals to the racemic, supercooled 1,1'-binaphthyl melt might be more effective than the mechanical mixing of solids. A series of experiments were performed to test this suggestion,

Table X

The Influence of Added Seed Crystals of Optically Active 1,1'-Binaphthyl on the Solid-State Resolution of Polycrystalline, Racemic 1,1'-Binaphthyl

Racemic Batch ^a	[α] of Seeds, degrees	Percent of Total Material Due to Seeds	[α] Produced, ^b degrees
B	+99	10	+55
F	+200	3	+112
G	"	0.9	+53
"	"	0.9	+91
"	"	0.7	+42
H	"	0.05	+62
I	-212	1.2	-20
"	"	1.6	-28
"	+204	3.4	-15

^a The total weight of each sample (except H) was between 10 and 20 mg. The sample taken from Racemic Batch H weighed 2.0 g. Its behaviour in the absence of artificial seeding was not checked.

^b After heating at 150° for at least one hour.

and the results are listed in Table XI, in the order in which they were obtained. Eight different samples of highly active 1,1'-binaphthyl were used as seeds. The supercooled melts were prepared by heating 0.2 g of racemic 1,1'-binaphthyl in a stoppered test tube at 170-190° for three minutes to destroy all solid forms of 1,1'-binaphthyl, then quickly

Table XI

The Influence of Optically Active 1,1'-Binaphthyl Seed Crystals on the Resolution by Crystallization from a Supercooled, Racemic 1,1'-Binaphthyl Melt

	[α] of Seeds, degrees	Number and Condition of Seeds	Temperature of Supercooled Melt, °C	[α], degrees ^b	
				A	B
1	+200	ca. 1 mg coarse powder	149.6	+205	+203
2	"	"	"	+126	+149
3	0	a few coarse granules	"	-7	-6
3	-7	"	"	+52	+22
4		none	"	-210	+214
6	+200	a few coarse granules	"	+176	+172
7	+204	"	135	0	
8	-212	"	"	0	
9	0	"	"	+1	
10	+204	"	140	0	
11		none	"	-9	-10
12	+204	a few coarse granules	145	+3	
13	"	"	149.6	+144	
14	-212	"	155	-183	-194
15	+204	"	149.6	+76	+73
16	-212	"	"	-1	+51
17	+204	one granule	"	+81	+77
18	-212	"	"	+25	+40
19	+204	"	145	+5	
20	"	"	"	-18	

(Table XI, continued)

21	+194	one granule	149.6	-73	-22
22	+204	"	"	+139	
23	+200	a few coarse granules	"	+196	+158
24	-212	<u>ca.</u> 1 mg fine powder	"	-42	-35
25	+200	one granule	145	+95	
26	-212	"	"	0	

^a Duplicate analyses on the same sample are listed under A and B.

immersing most of the tube in a thermostatted silicone oil bath (usually held at 150°). The seeding crystals of 1,1'-binaphthyl, which varied from a single particle to a fine powder, were then added to the supercooled melt. The tubes were stoppered while the solid 1,1'-binaphthyl grew (usually, overnight), to try to eliminate laboratory dust.

Some experiments were very successful in producing 1,1'-binaphthyl having $[\alpha] > 200^\circ$. However, attempts to reproduce these successful experiments usually failed. The duplicate analyses show that some individual samples were quite inhomogeneous in activity, implying that the added seeds could not always control the crystallization of the entire melt. Unintentional seeding probably accounts for the lack of reproducibility, since even "unseeded" samples eventually crystallized.

Inadvertent seeding can be eliminated by performing the crystallizations in sealed ampules. In fact, using a special procedure, all 1,1'-binaphthyl seeds can be eliminated, and the resolution by crystallization can be performed spontaneously. Because of their special

interest, the results of these extensive experiments are reported in Section 3.6. For the present discussion, we shall simply state that this method does not consistently produce highly active 1,1'-binaphthyl.

Because several other systems have been successfully resolved by seeding a supersaturated solution,⁸⁵ this additional method was also tried with 1,1'-binaphthyl. By means of a special experimental procedure which we developed, a single seed having $[\alpha] = -212^\circ$ was placed in contact with a filtered, supersaturated solution of 1,1'-binaphthyl in 2-propanol at 120° (sealed tube). Crystals developed, but analysis gave $[\alpha] = -2^\circ$, indeed a poor result. A second attempt was made, this time using a high-speed stirrer to disperse finely ground seed crystals ($[\alpha] = -194^\circ$) in a supersaturated solution with ethylene glycol. The resulting activity of the precipitated material was, however, only $[\alpha] = -38^\circ$. No further attempts to seed out optically active 1,1'-binaphthyl from solution were made.

3.4.3 The Behaviour of Partially Active Solid 1,1'-Binaphthyl

Evidently, the mechanical addition of seed crystals to racemic 1,1'-binaphthyl (in solid, liquid and solution phases) is a poor method of reproducibly preparing highly optically active material. This is probably due to the fact that in these experiments, the effect of the seeds is not "felt" by the bulk of the sample, in spite of efforts to obtain (manually) a good distribution of the seed crystals. A far more intimate mixture is apparently required.

The best method of mixing optically active and racemic 1,1'-binaphthyl is to dissolve both in a suitable solvent then recrystallize

the partially active material. In effect, this was performed in the original cycling experiments (Section 3.2, p 49), but not all of the recrystallized batches would resolve well on heating. This failure may have been due to the fact that not all of the partially active samples were in their most stable state at room temperature (i.e., racemate plus crystals of only one enantiomer), as discussed in Section 3.3.2.1 (p 64). We now turn our attention to the achievement of this most stable state, and the possibility of reproducibly preparing that highly stereospecific batch of 1,1'-binaphthyl which will resolve completely in a single heating.

A sample which is not in its most stable state would be expected to have too high a eutectic phase content, and the approach to this state is identical with the conversion of all racemic material in the sample to the racemate, leaving only racemate and crystals of the desired enantiomer. Such a solid-state conversion, if it occurs at all, is certainly very sluggish at room temperature.

Slow solid-solid transformations can be speeded up through the use of solution phase transformations.^{81d} Results of the solution phase transformation racemate \rightarrow solution \rightarrow eutectic form, which occurs above 70°, have already been reported (Section 3.4.1, p 83). In these experiments, we had hoped that the presence of a solution might improve the actual resolution process. If the reverse transformation (racemic eutectic \rightarrow solution \rightarrow racemate) can be effected at room temperature (see Figure 16, p 89), it might be possible to prepare good starting material for the solid-state resolutions.

To test the possibility of such a transformation, we attempted to

produce racemate from both partially active and almost racemic eutectic form in two separate experiments. However, even after vigorous stirring of the pulverized eutectic samples in contact with pentane at room temperature for up to three days, and after seeding the mixture with crystals of racemate, no transformation was observed. Cooling the rapidly-stirring mixture to -78° and changing solvents to methanol also has absolutely no effect.

The failure of this solution phase transformation may cast some doubt on the conclusion from phase studies that the racemate is the stable form of racemic 1,1'-binaphthyl at room temperature and below. However this negative evidence is not enlightening, since even solution phase transformations may be slow, especially if the difference in solubilities of the two forms is slight.^{81d}

The best method of producing the racemate, in spite of its unpredictable results, is recrystallization from solution. We had originally recrystallized from boiling pentane (36°), since losses in rotation at this temperature were slight. Low temperature recrystallizations (-78°) from acetone, used in the limit of resolution studies (Appendix A, p 178), can be carried out with virtually no losses in activity by solution racemization, and we next explored this as a method of preparing 1,1'-binaphthyl which might resolve well on heating.

The procedure we followed involved making an almost saturated solution of partially active ($[\alpha] = \pm 10^{\circ}$) 1,1'-binaphthyl in acetone at room temperature. This solution was carefully filtered then placed in a Dry Ice-acetone bath, where fine crystals appeared in about ten minutes. After 30 minutes to one hour, crystallization seemed complete, and rapid

filtration while cold gave ca. 80% material. The first such recrystallization we tried was perfectly successful; crystals having an activity of $[\alpha] = +0.8^\circ$ resolved, on heating at 150° overnight, to $[\alpha] = +209^\circ$. This represented the largest increment in optical rotation we had yet observed. A second experiment, repeating exactly the procedure of the first, was also successful; material of activity $[\alpha] = +0.3^\circ$ gave $[\alpha] = +205^\circ$ on heating. The procedure seemed reproducible. A third experiment was performed on a larger amount (4 g) of 1,1'-binaphthyl and it, too, produced 80% material, $[\alpha] = +1.4^\circ$, which could increase to $[\alpha] = +211^\circ$ on heating at 150° . This large batch of resolvable 1,1'-binaphthyl was used in a kinetic study (as Kinetic Batch S-1, Section 3.5), from which it was learned that even at 105° , resolution to $[\alpha] = +221^\circ$ was possible.

A fourth low temperature recrystallization was an attempt to obtain 1,1'-binaphthyl which would give high negative rotations on heating. Much to our disappointment, the attempt failed, and only $[\alpha] = -31^\circ$ was attained on heating at 135° overnight. Apparently we had unknowingly changed some parameter to which the recrystallization procedure is rather sensitive. We then set out to determine the extent to which our original successful procedure could be altered. Sixteen more recrystallizations were performed and several factors were varied: the activity of the solution of 1,1'-binaphthyl from which recrystallization occurred, from $[\alpha] = 0$ to $[\alpha] = 71^\circ$; the concentration of 1,1'-binaphthyl in this solution, from 1.43 g / 100 ml acetone (saturated) to 0.67 g / 100 ml acetone; and the time allowed for recrystallization at -78° , from 15 min to 12 h. Also varied were such qualitative factors as agitation while recrystallization occurred, methods of filtration, purity of acetone solvent (distilled or

undistilled), and seeding with various forms of 1,1'-binaphthyl (both active and racemic). In all of these experiments, poor results were obtained. Even very careful attempts to reproduce the original procedure failed. We can offer no explanation as to why the first three recrystallizations worked perfectly, and the ensuing sixteen did not succeed. Perhaps the preparation of resolvable 1,1'-binaphthyl by this method is governed by delicate kinetic factors, which are difficult to control experimentally.

At this time we discovered, somewhat by accident, a method which has produced highly resolvable 1,1'-binaphthyl every time. In the course of cycling a quantity of 1,1'-binaphthyl to high rotations, we recrystallized an acetone solution of $[\alpha] = +10^\circ$ material at -78° (hoping to obtain crystals which would produce at least some activity on heating), then, to conserve material, we did not filter the crystals from the solution, but instead distilled off the acetone under reduced pressure at 25° . The material obtained ($[\alpha] = -9.5^\circ$) resolved to $[\alpha] = -216^\circ$ on heating at 150° for 16 h. An extensive investigation of this recrystallization-evaporation procedure was conducted. Twenty-seven experiments were performed, sixteen of which were reproducibility checks and preparations of highly resolvable 1,1'-binaphthyl, and eleven of which were variations on this successful procedure. Of the sixteen repetitions, fifteen gave material which would resolve to greater than $[\alpha] = 190^\circ$ (78% resolution) on heating at 150° .

The successful recrystallization-evaporation procedure, summarized here for discussion and given in detail in Section 4.3.2.3 (b), p 158), is easy to perform. The method involves dissolving 1,1'-binaphthyl of

$[\alpha] = 2^\circ$ to 15° in distilled acetone (1.2 g / 100 ml), filtering the solution, then swirling it in a Dry Ice-acetone bath until crystals appear (about 15 min). The cold flask is then placed on the rotary evaporator and the vacuum (water aspirator) applied. When the greatest vacuum is attained, the cold flask is lowered into a bath at $20-25^\circ$. As the flask warms, the crystals begin to dissolve and the acetone begins to distill off. These two processes (warming and loss of solvent) oppositely affect the amount of 1,1'-binaphthyl in solution, and most (but not all) of the crystals dissolve at one point, whereafter they come back out of solution as the loss of solvent continues. Eventually (in about 30 min), all the solvent disappears, and the remaining crystals will resolve well on heating.

Straight evaporation of a solution of 1,1'-binaphthyl gives poor results. Also, for the procedure to succeed, the crystals must not totally dissolve during the evaporation. Partial evaporation of solvent followed by filtration gives unpredictable results.

The success of this procedure evidently depends on the presence, during the evaporation of a slightly active solution of binaphthyl, of suitable seed crystals. These "correct" seeds are generated during the warming of a cold mixture of solid material plus solution to room temperature. The fact that almost all crystals disappear during the evaporation implies that those which dissolve are "undesired" seeds, the "correct" seed crystals remaining behind to induce the further growth of resolvable 1,1'-binaphthyl.

A possible explanation for this phenomenon lies in a consideration of the ternary system involved. When a pair of enantiomers forms a racemate, the ternary phase diagram between R, S and optically inactive

solvent appears as in Figure 17 at any constant temperature which is above the melting point of the solvent and below that of the enantiomers.^{45d,53,85} Figure 17 (a) is a schematic representation of the ternary system at -78° , and Figure 17 (b) represents the same at 25° . The solid lines are the stable phase boundaries. In Figure 17 (b) the one- two- and three-phase regions are labelled. In both diagrams, the dotted lines represent metastable extrapolations of the solubility curves of solid R, racemate, and solid S.

Point y represents (schematically) the overall composition of the slightly active S-1,1'-binaphthyl solution at the beginning of the recrystallization-evaporation procedure. At 25° , it is seen to lie in the one-phase solution region, since all solid 1,1'-binaphthyl dissolves at this temperature. At -78° , however, it lies formally in the three-phase S + racemate + solution region, so that these two solid phases can separate from the solution. In addition, it probably lies behind the solubility curves of all three solid phases, and the material which crystallizes likely contains R, S, and racemate together. On rewarming to 25° (on the rotary evaporator), all three phases will begin to dissolve as the system approaches that in Figure 17 (b). However, since the point y now lies farthest from the R solubility curve, this form can dissolve first and fastest, leaving behind only S and racemate to seed out the 1,1'-binaphthyl in solution as the evaporation proceeds. The solid material thus obtained probably consists only of racemate and S crystals, the long-sought phase mixture which is ideally suited for resolution at higher temperatures.

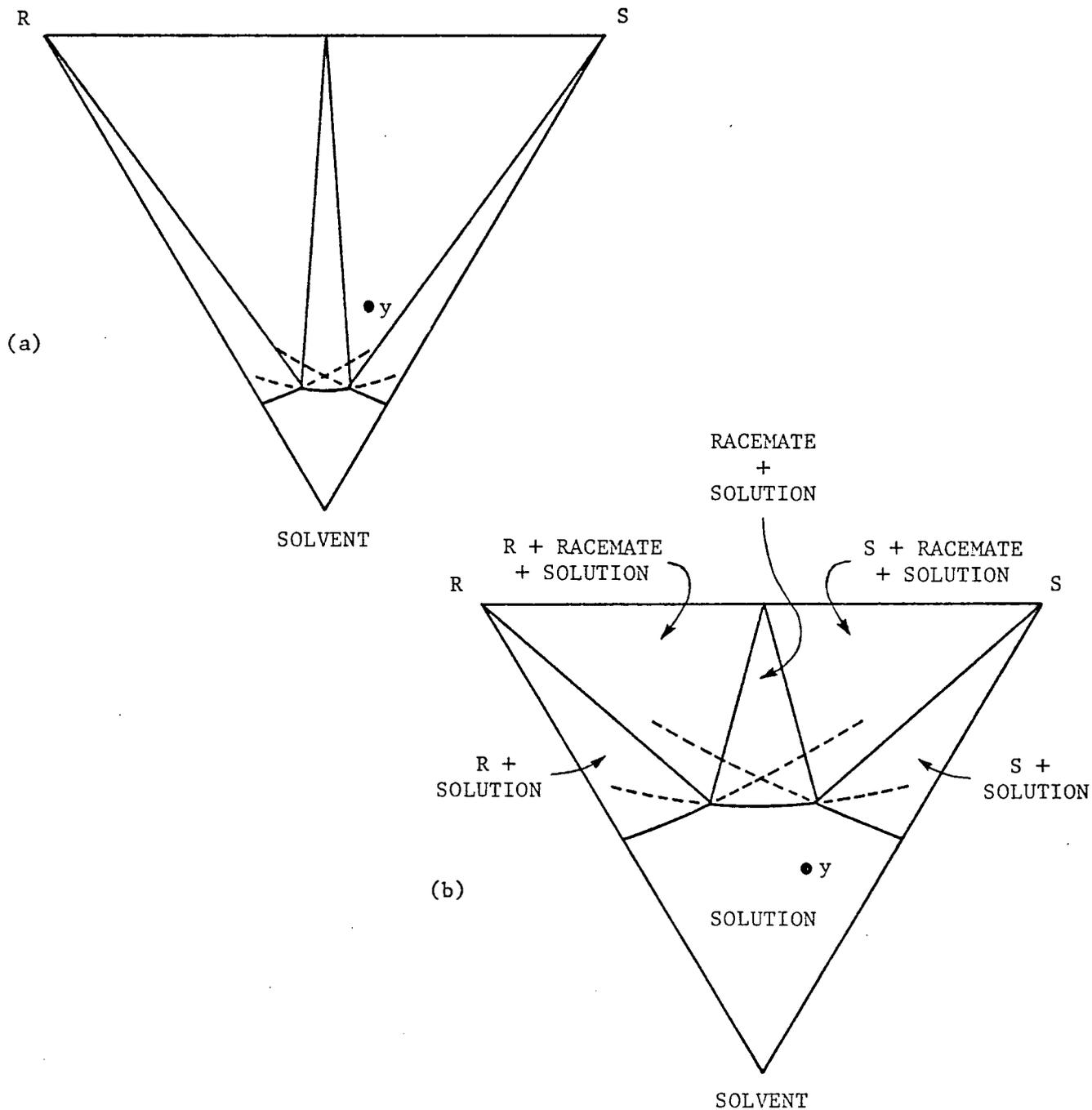


Figure 17. Schematic representation of the ternary system formed between solvent, R- and S-1,1'-binaphthyl. Metastable extrapolations of phase boundaries (solubility curves) are shown as dotted lines.

(a) Temperature: -78° , (b) Temperature: $+25^\circ$.

3.5 Kinetic Study of the Solid-State Resolution

Once a method of preparing solid 1,1'-binaphthyl which would resolve consistently to a high specific rotation had been found, a kinetic investigation of the resolution process became possible. Four different batches of resolvable 1,1'-binaphthyl were used in the kinetic study - three producing S-(+)-1,1'-binaphthyl and one giving R-(-)-1,1'-binaphthyl on heating. The first kinetic batch, S-1, consisted of 3.0 g of material acquired by a simple low temperature recrystallization from acetone (p 98). The others (S-2, 4.0 g; S-3, 5.7 g; and R-1, 3.8 g) were prepared from the successful recrystallization-evaporation procedure (p 99).

3.5.1 The Development of Optical Activity with Time

The resolution reaction of each batch was followed by heating individual sealed ampules containing a carefully weighed amount (15-20 mg) of the polycrystalline 1,1'-binaphthyl at a given temperature for various lengths of time. Some representative specific rotation-time plots are shown in Figures 18-22. Kinetic runs were performed at four temperatures - 135°, 125°, 115°, and 105° - for all kinetic batches except S-1, which was explored only at 135° and 105°. The final specific rotations, $[\alpha]_F$, of each of these runs are listed in Table XII. All batches resolved to greater than $[\alpha] = \pm 200^\circ$ at 150°, but with a half-life too short for an accurate kinetic description.

Several comments should be made regarding the form of the kinetic curves. What is immediately obvious is the smoothness to the kinetic points - much more satisfactory for kinetic analysis than the scatter

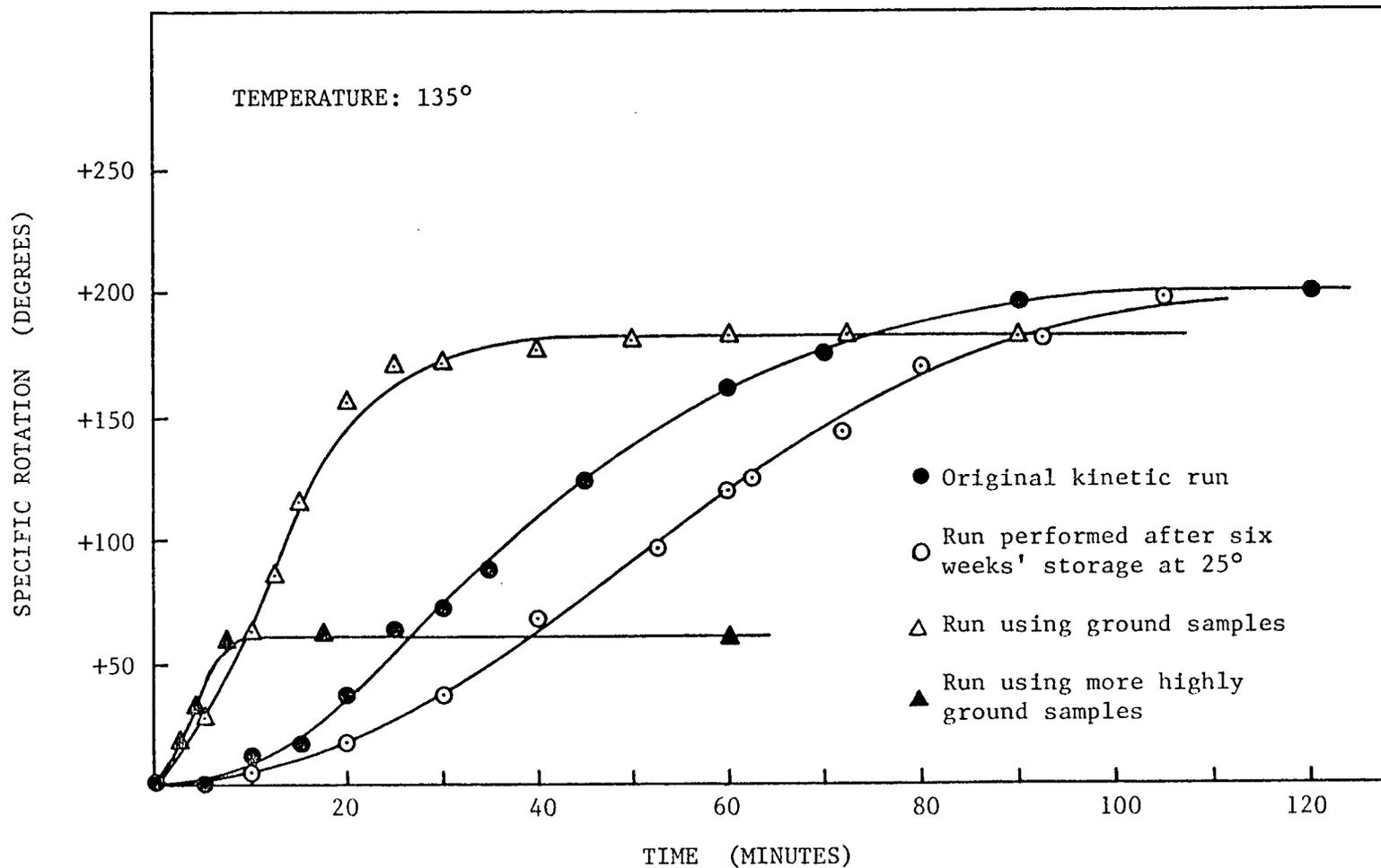


Figure 18. Kinetic data for the solid-state resolution of neat, polycrystalline 1,1'-binaphthyl, S-1 Kinetic Batch at 135°. Effect of grinding and of storage at 25° for six weeks.

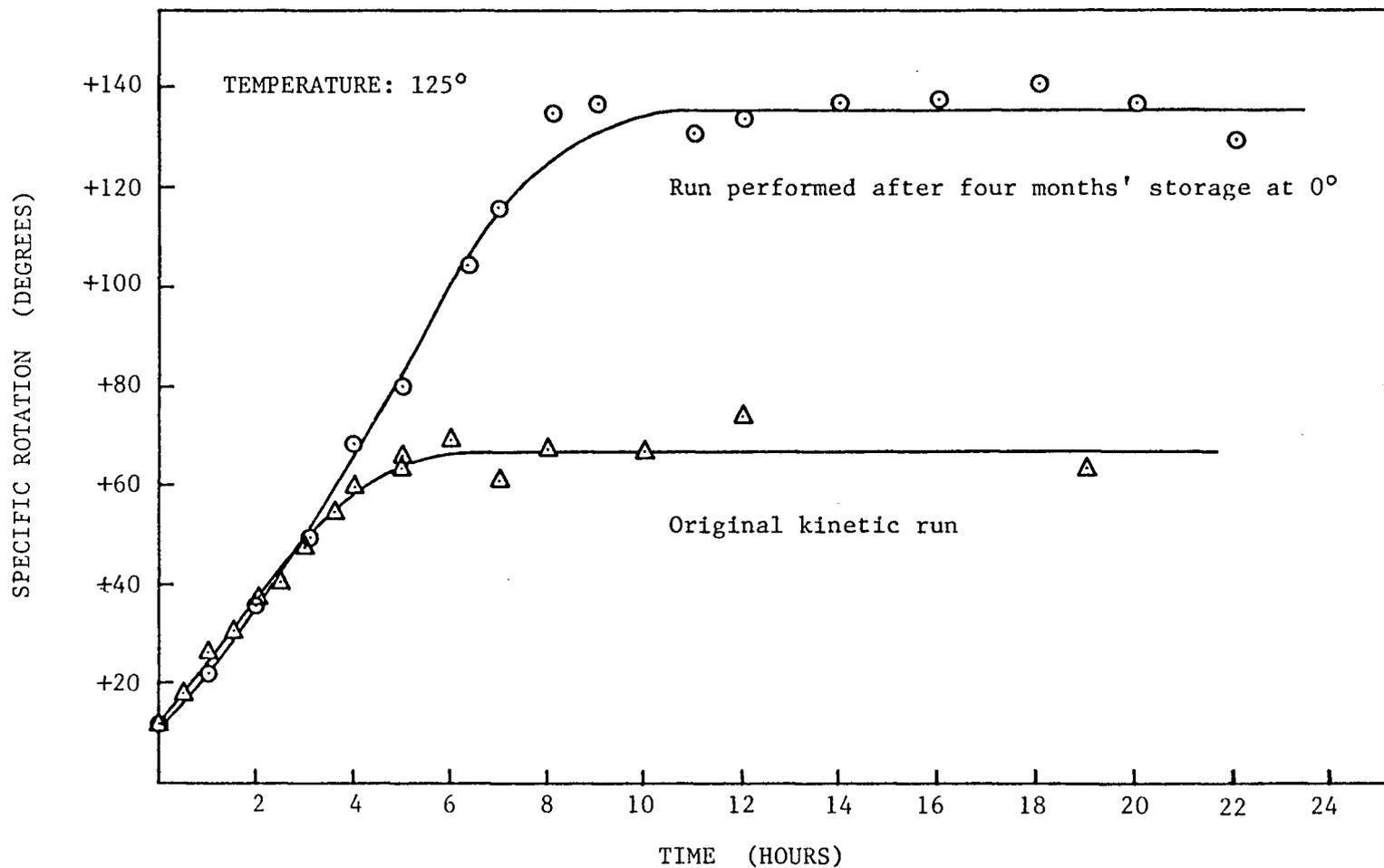


Figure 19. Kinetic data for the solid-state resolution of neat, polycrystalline 1,1'-binaphthyl, S-2 Kinetic Batch at 125°. Effect of storage of samples at 0° for four months.

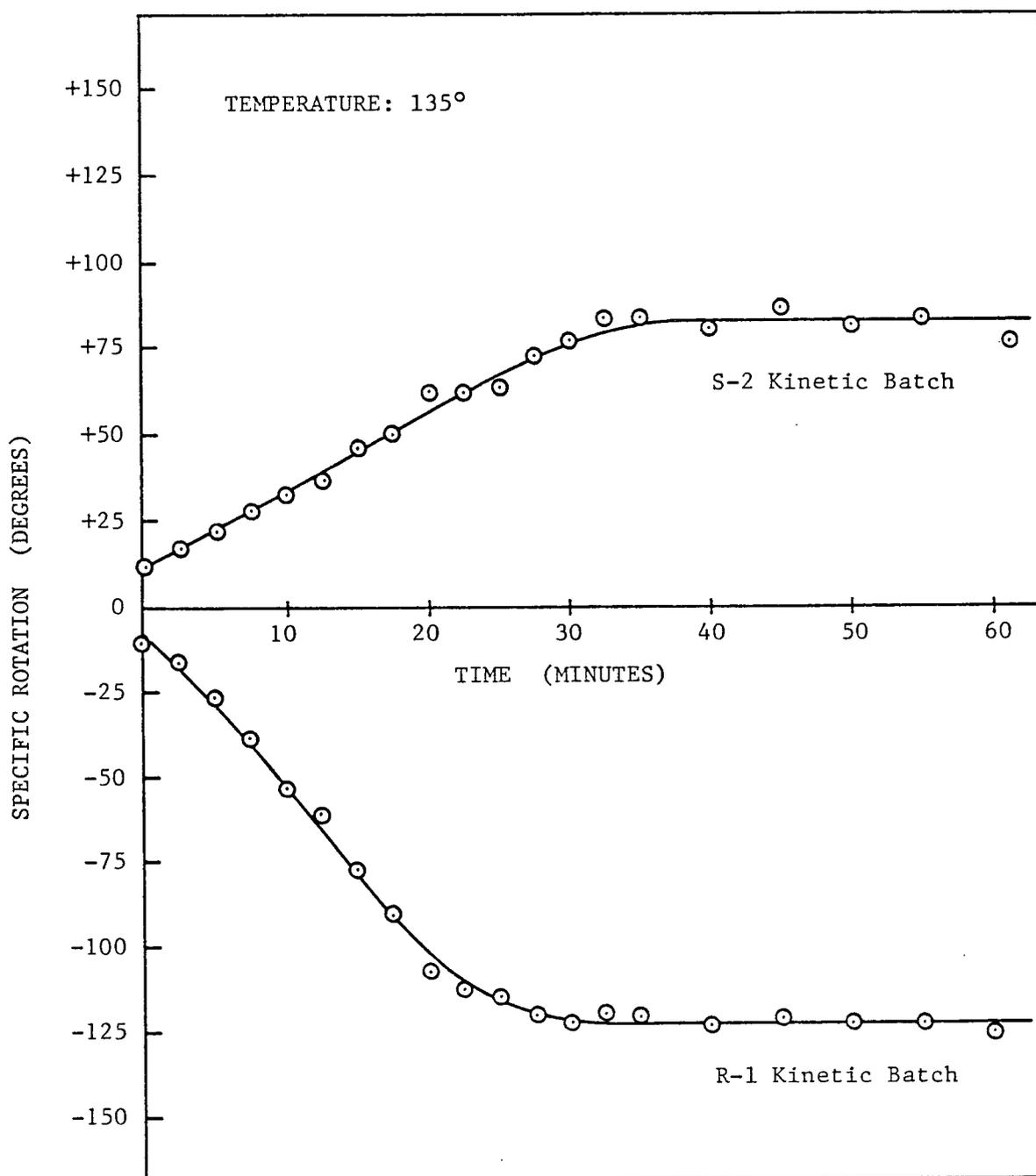


Figure 20. Kinetic data for the solid-state resolution of neat, polycrystalline 1,1'-binaphthyl, S-2 and R-1 Kinetic Batches at 135°.

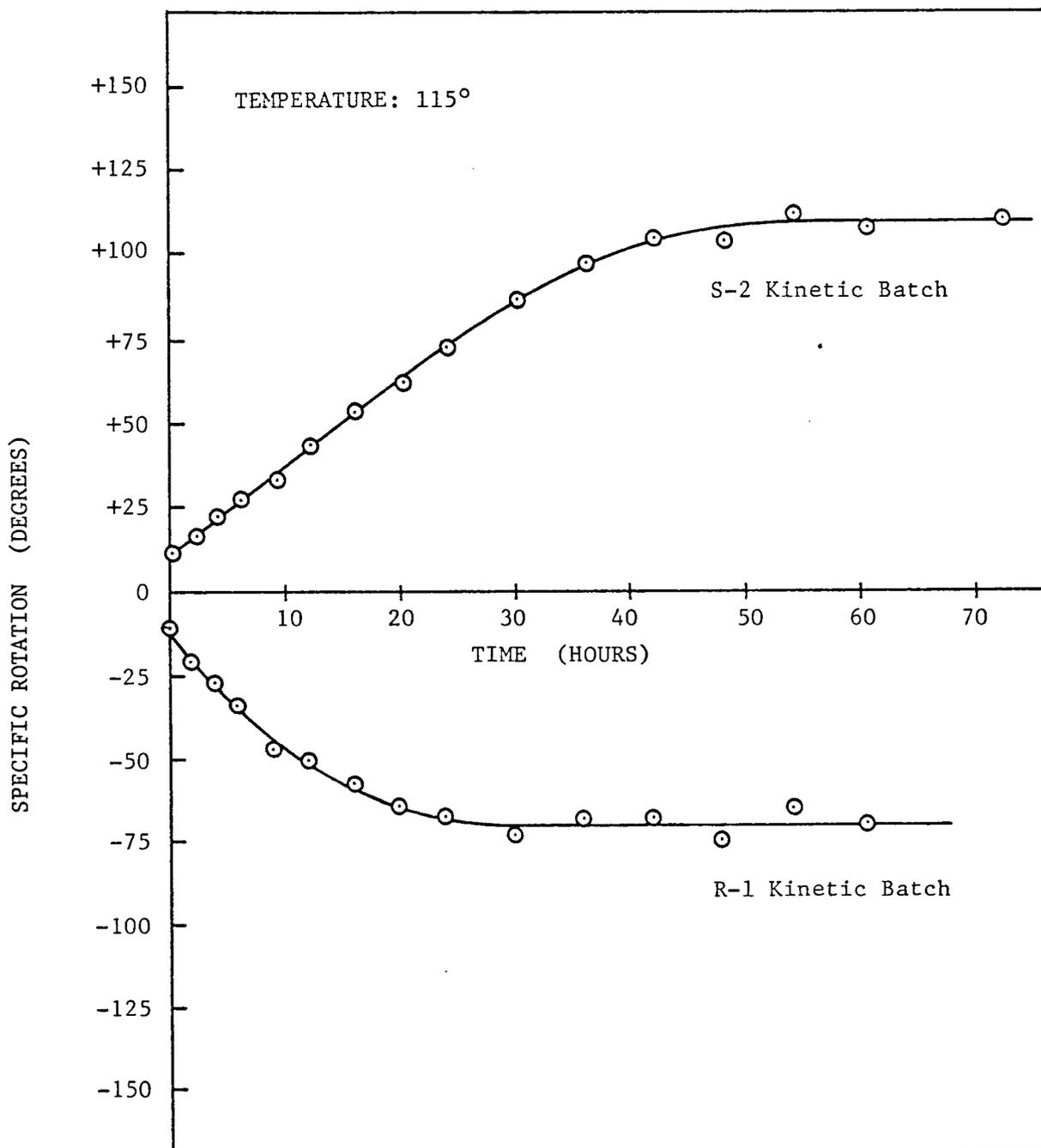
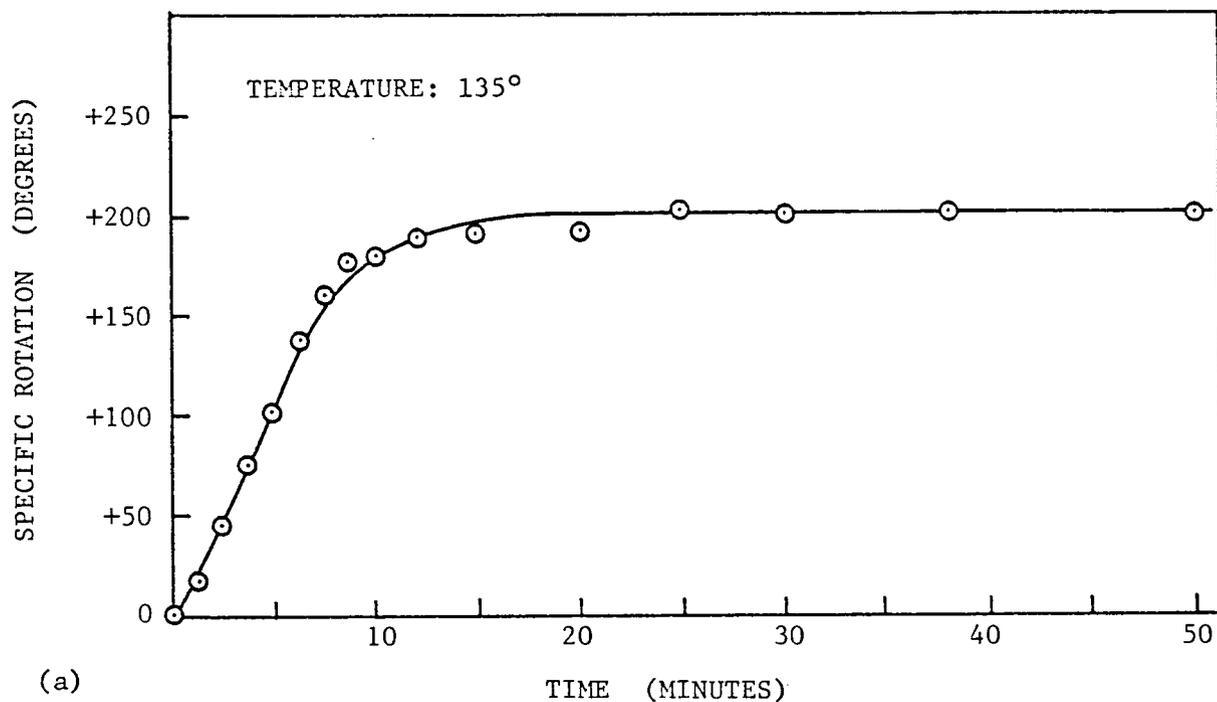
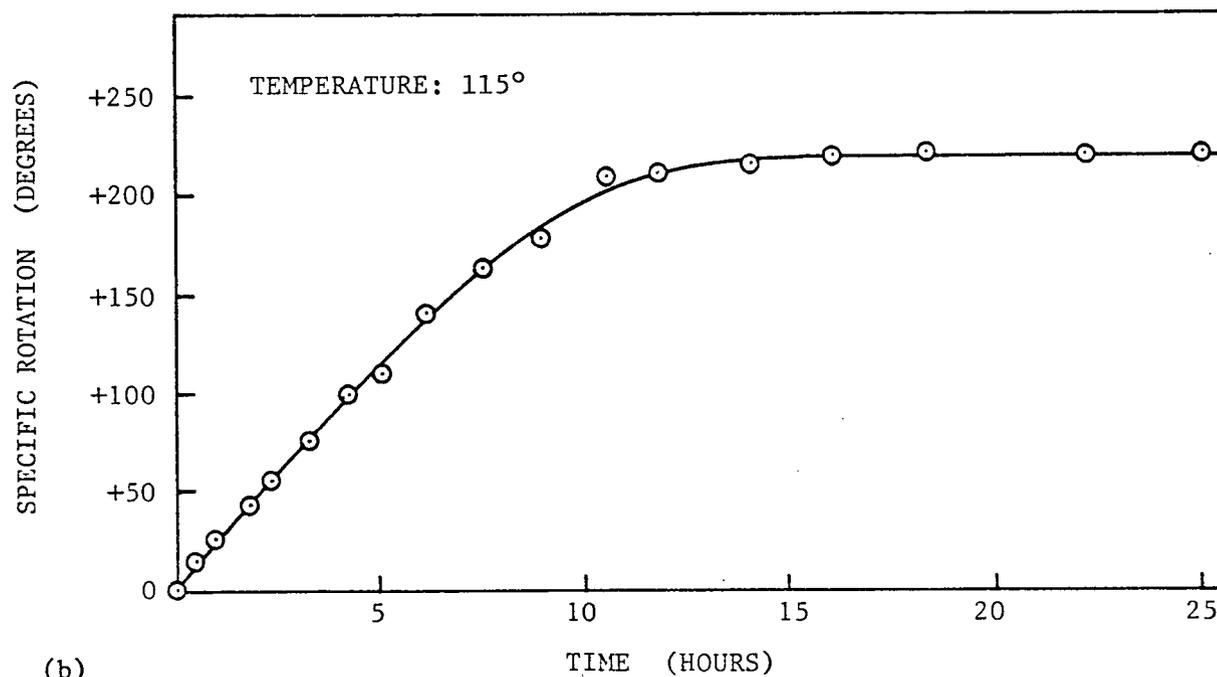


Figure 21. Kinetic data for the solid-state resolution of neat, polycrystalline 1,1'-binaphthyl, S-2 and R-1 Kinetic Batches at 115°.



(a)



(b)

Figure 22. Kinetic data for the solid-state resolution of neat, polycrystalline 1,1'-binaphthyl, S-3 Kinetic Batch at (a) 135° and (b) 115°.

Table XII

Final Specific Rotations in the Solid-State Resolution of 1,1'-Binaphthyl
(Kinetic Batches)

Kinetic Batch	Temperature, °C	$[\alpha]_F$, degrees	Half-Life ^a
S-1	149.6	+211	25 min
"	135.0	+201	37 min
"	135.0 ^b	+201	53 min
"	135.0 ^d	+182	13 min
"	135.0 ^e	+61	3 min
"	105.1	+221	6.6 days
S-2	149.6	+226	<1 min
"	135.0	+84	14 min
"	124.9	+67	1.7 h
"	124.9 ^c	+136	4 h
"	114.9	+110	17 h
"	105.1	+123	4.3 days
S-3	149.6	+200	<1 min
"	135.0	+201	5 min
"	124.9	+214	38 min
"	114.9	+223	5 h
"	105.1	+229	1.1 days
R-1	149.6	-233	<1 min
"	135.0	-123	13 min
"	124.9	-71	1.2 h
"	114.9	-69	6 h
"	105.1	-79	1.7 days

- a Time taken to achieve $[\alpha]_D/2$.
- b Run performed after six weeks' storage at 25°.
- c Run performed after four months' storage at 0°.
- d Run using ground samples.
- e Run using more highly ground samples.

obtained when racemic 1,1'-binaphthyl is heated (Figure 15, p 86). Although the activity develops smoothly, there appears to be no characteristic shape to the curves. Some are sigmoid (although none have prolonged induction periods), and others appear to increase linearly with time or even show a rate maximum at the start of the run. The extent of resolution also varies. Contrary to the very high rotations achieved at 150°, the S-2 and R-1 Kinetic Batches suffer a loss in resolving ability at lower temperatures.

The kinetic runs are also sensitive to grinding or to storage for any great length of time. As demonstrated with the S-1 sample at 135°, the act of grinding the starting material causes a faster resolution to a lower specific rotation (Figure 18). Also, the S-1 Kinetic Batch did not show the same kinetics before and after storage for six weeks at room temperature (25°). Instead, the resolution was slowed somewhat, although the extent of resolution was preserved. For this reason the kinetics of this batch were not explored at 115° or 125°. The others were stored at 0° while the kinetic runs were performed (within five weeks). A reproducibility check of the S-2 Kinetic Batch was performed after four months' storage at 0° (Figure 19), and showed an unchanged rate of resolution but an enhanced extent of resolution (originally, to

$[\alpha] = +67^\circ$; after four months, to $[\alpha] = 136^\circ$). Therefore, the value of $[\alpha]_F$ will have altered to some extent during the five weeks taken for the kinetic runs, but any changes in the rate of resolution are probably small. There is some value in neglecting these changes to allow an analysis in terms of known rate equations for solid-state reactions. This will be done in Section 3.5.2.

Some samples of the fastest-resolving batch (S-3) were ground (to accelerate the reaction even further) and heated at temperatures below 105° , to establish the lowest temperature at which the resolution can proceed. The results are organized in Table XIII. Even at 98° , samples

Table XIII

Low Temperature Solid-State Resolution of 1,1'-Binaphthyl

Temperature, $^\circ\text{C}$	Time, weeks	$[\alpha]$, degrees	Kinetic Batch
97.7	0	+1.4	S-1
"	2.6	+9	"
"	11.2	+156	"
"	24.9	+227	"
93.0	0	+1.8	S-3, ground
"	1.0	+67	"
"	3.7	+114	"
"	4.0	+125	"
87.6	0	+1.8	"
"	1.0	+33	"
"	3.7	+64	"
"	4.0	+77	"

(Table XIII, continued)

83.3	0	+1.8	S-3, ground
"	1.0	+16	"
"	4.0	+26	"
76.9	0	+1.8	"
"	1.0	+5.8	"
"	4.0	+11	"
"	25.5	+22	"
64.2	0	+1.8	"
"	1.0	+1.9	"
"	4.0	+1.2	"
"	25.5	0	"

are capable of resolving to high rotations, but considerable lengths of time are required. The lowest temperature at which an increase in specific rotation is observable is 76° , where $[\alpha] = +22^{\circ}$ was achieved after six months. No reaction was discernable at 64° , even after half a year.

The absence of resolution at 64° could imply that this temperature is lower than the solid-solid transition temperature τ (Figure 11 (d), p 67). However, caution should be used in making such a conclusion, in view of the slowness of the resolution at 76° . It is best simply to state that the low temperature kinetic results indicate that τ is lower than 76° .

From the results given above it is obvious that the kinetic behaviour of the solid-state resolution of 1,1'-binaphthyl is considerably more

complex than the simple first-order solid-state racemization of the diacid 29 reported in Section 2 of this thesis. Such a kinetic complexity is to be expected, considering the nature of the processes involved in the reaction. The resolution is caused by the stereospecific growth of crystals of one enantiomer at the expense of the racemate phase. Such a process would be highly dependent on the area of the interface between the solid reactant phase and the solid product phase. Any procedure which can change the area of this interface in the starting material will greatly affect the observed rate of reaction.⁵⁸

The fact that an entire sample of almost-racemic 1,1'-binaphthyl can convert to essentially only one enantiomer means, of course, that enantiomer interconversion must occur somewhere in the sample. At 150°, where the racemate melts, leaving behind crystals of only one enantiomer, racemization occurs very rapidly (with a half-life of less than 0.5 sec in the melt). Growing S crystals (for example) can select S molecules from a melt which is essentially always racemic (while it lasts). In the temperature range 76° to 135°, where the sample is entirely solid, enantiomer interconversion (a simple conformational change) can conceivably occur in the interface between growing S crystals and the disappearing racemate crystals. In a polycrystalline sample, this interface will be very extensive. Since the reactant-product interface represents an area of contact between centrosymmetric (racemate) and noncentrosymmetric (pure enantiomer) crystals, it will be quite disorganized ("incoherent")^{87a} The higher (surface) free energy associated with this part of the solid state could well facilitate enantiomer interconversion, making possible the solid-state resolution.

If the interconversion of enantiomers in the reactant-product interface is very fast compared to the rate of growth of crystals of pure enantiomer, then the reaction is essentially only a phase change. Phase changes are almost always governed by nucleation-and-growth processes.⁶¹ That is, not only can a phase transformation occur via growth of small crystallites of product which exist initially in the reactant phase, but new crystallites can form (nucleate) during the phase change. Up to this point, we have considered only the growth of "seed" crystals of pure enantiomer present initially in the solid sample of 1,1'-binaphthyl. Indeed, the elimination of crystals of "unwanted" enantiomer was the prime objective in the designing of experiments to produce resolvable 1,1'-binaphthyl. However, as will be seen, the kinetic results require a consideration of the nucleation of new eutectic crystals from the reacting racemate phase.

The prospect of nucleation in the R,S-1,1'-binaphthyl phase system carries with it some interesting stereochemical consequences. According to the classical theory of nucleation,^{61,87b} new crystals are formed from local statistical fluctuations in energy, concentration, and orientation of molecules in the reactant phase. But in the 1,1'-binaphthyl system, the reactant phase is a racemic crystal below 145° or a racemic melt between 145° and 158°. This means that the local fluctuations are just as likely to involve R molecules as S molecules. In other words, nucleation in the racemic phase is expected to create both R and S crystallites with equal probability. This will be true regardless of the sites of nucleation in the reactant crystal. Whether nucleation is homogeneous - occurring at all points in the reactant crystal with equal

likelihood - or whether it occurs only at defects, dislocations or boundaries between reactant crystallites, the overall products of nucleation should be a racemic, eutectic mixture of individual R and S crystallites. A racemic reactant phase will show no preference for the formation of any one enantiomer.

The reasons for the failure of some batches of 1,1'-binaphthyl to resolve well on heating are therefore: (a) the presence of crystallites of both enantiomers in the initial material before heating, (b) the nucleation of racemic material during the reaction, or (c) both.

The kinetic results provide an opportunity to test these reasons for failure, since we know the conditions under which the high resolvability of the batches can be destroyed. For example, grinding the S-1 Kinetic Batch causes a faster resolution, but to a lower rotation. Certainly, grinding will break apart the S crystallites present initially in the material (and imparting a small specific rotation of $[\alpha] = +1.4^\circ$), creating a greater reactant-product interface and causing a more rapid reaction. In addition, R crystallites are either formed during the grinding process or nucleated (along with an equal number of S crystallites) when the ground sample was heated. The fact that the racemate has a lower molar volume ($196.2 \text{ ml mole}^{-1}$)ⁿ than the eutectic form ($214\text{-}216 \text{ ml mole}^{-1}$)^o implies that the pressure of grinding could not cause a phase

ⁿ Calculated from the crystallographic data of Kerr and Robertson⁷⁷ for the low-melting form of 1,1'-binaphthyl.

^o Extrapolated to 25° from the dilatometric data of Binns and Squire⁸² for the high-melting form of 1,1'-binaphthyl between 120° and 158° .

change from the racemate to an equimolar mixture of R and S crystals. Hence the sample, both before and after grinding, very likely contained essentially only S crystals and racemate crystals, the R form being nucleated (along with S) more readily from the ground sample. The reason for the decreased extent of resolution in ground samples may then be that grinding creates stresses, dislocations, and other imperfections in the reactant lattice, and these can act as sites for the nucleation of racemic material.

Also, the S-2 and R-1 Kinetic Batches resolved rather poorly in the temperature range 105-135° (where the reactant phase is the racemate) and excellently at 150° (where the reactant phase is the melt). If the poor resolvability at 105-135° is due to the initial presence of both R and S crystallites, then one would expect the growth of both forms also at 150°, which is not the case. A more tenable explanation involves the nucleation of racemic material from the racemate phase, but not from the melt phase. As mentioned earlier, the 1,1'-binaphthyl melt supercools to a great extent, and completely melted samples will remain at 150° indefinitely without crystallization, unless crystals are intentionally added. Although growth on seed crystals occurs readily at 150°, nucleation of new crystals does not. Therefore a high degree of resolution may occur at 150° but not at 105-135°.

The S-1 and S-3 Kinetic Batches resolve to greater than 82% resolution at all temperatures studied. The failure to attain total resolution ($[\alpha] = \pm 245^\circ$) in these batches is probably due to crystals of unwanted R enantiomer present initially, rather than to nucleation, since there is no improvement in resolution with these samples at 150°, where

nucleation is absent.

The changes on storage of the S-2 Kinetic Batch over several months is consistent both with nucleation and with the presence of unwanted enantiomer. On one hand, the improved extent of resolution of the S-2 material on storage could be due to the partial annealing out of the crystal imperfections and boundaries causing nucleation of racemic material. Annealing is made possible by the relief of surface and strain free energies in the polycrystalline sample. On the other hand, the presence of unwanted enantiomer could be diminished by a very slow phase transformation at 0°, converting racemic eutectic form back to the racemate.

The secret to preparing 1,1'-binaphthyl which will resolve well on heating at all temperatures evidently involves minimizing not only the crystals of unwanted enantiomer, but also the tendency of the racemate to nucleate racemic, eutectic form. Although the latter requirement is difficult to control, it can be avoided simply by performing the resolution at 150°, where the racemate melts, and all batches of 1,1'-binaphthyl prepared by the special recrystallization-evaporation procedure (p 99) attain a very high degree of resolution.

3.5.2 Treatment of Results in Terms of Rate Laws for Solid-State Reactions

Although some qualitative conclusions can be drawn from the kinetic results (Section 3.5.1), a more quantitative treatment can potentially provide insight into the mechanism and energies involved in the solid-state resolution.

As will be seen, the rate equations which have been developed for solid-state reactions involve an expression of y , the fraction transformed, as a function of time. In this resolution reaction, the fraction transformed is conveniently taken as the extent of the phase transformation racemate \rightarrow eutectic form, regardless of the final rotation achieved. That is, $y = X_H$, where X_H is the mole fraction of 1,1'-binaphthyl in the eutectic (high-melting) form. Although $X_H = 1$ at the end of the transformation, it is close to but not exactly zero at the beginning, since some small seed crystals of eutectic form exist in the initial material. Hence, before the reaction, the material is considered as already slightly transformed.

During the resolution, $[\alpha]$ was measured as a function of time, until a final rotation, $[\alpha]_F$, was attained. Intuitively, it would seem that $[\alpha]/[\alpha]_F = X_H$, but the conditions under which this equality will hold should be examined more closely.

In any batch of 1,1'-binaphthyl, the only phases present are the racemate, crystals of R, and crystals of S. The last two constitute the eutectic form. It is convenient to define the following:

- X_R (or X_S) = mole fraction of R (or S) in all phases
 X_{R-H} (or X_{S-H}) = mole fraction of R (or S) in eutectic (high-melting) form
 X_{R-L} (or X_{S-L}) = mole fraction of R (or S) in racemate (low-melting) form
 X_{R-F} (or X_{S-F}) = mole fraction of R (or S) at end of transformation

The specific rotation of the sample at all times is:

$$[15] \quad [\alpha] = [\alpha]_S(X_S - X_R) = [\alpha]_R(X_R - X_S)$$

where $[\alpha]_S = +245^\circ$, and $[\alpha]_R = -245^\circ$, the specific rotations of completely resolved S and R-1,1'-binaphthyl, respectively. But since the racemate contains an equimolar quantity of S and R-1,1'-binaphthyl, i.e., $X_{S-L} = X_{R-L}$, and since $X_S = X_{S-H} + X_{S-L}$ and $X_R = X_{R-L} + X_{R-H}$ then the difference in mole fractions of S- and R-1,1'-binaphthyl in all phases is identical to that only in the eutectic form ($X_S - X_R = X_{S-H} - X_{R-H}$) and so it is always true that:

$$[16] \quad [\alpha] = [\alpha]_S (X_{S-H} - X_{R-H})$$

At the end of the transformation, $X_{S-H} = X_{S-F}$ and $X_{R-H} = X_{R-F}$, so that:

$$[17] \quad [\alpha]_F = [\alpha]_S (X_{S-F} - X_{R-F})$$

Therefore, in all batches of polycrystalline 1,1'-binaphthyl,

$$[18] \quad \frac{[\alpha]}{[\alpha]_F} = \frac{X_{S-H} - X_{R-H}}{X_{S-F} - X_{R-F}}$$

Consider now a hypothetical sample of 1,1'-binaphthyl which resolves perfectly. If the resolution is to pure S-enantiomer, then $[\alpha]_F = [\alpha]_S$. In such a resolution, no nucleation of racemic material would occur, and the eutectic form would always consist only of growing S crystals.

Therefore, $X_{S-H} = X_H$, $X_{R-H} = X_{R-F} = 0$, $X_{S-F} = 1$, and Equation 18 becomes:

$$[19] \quad \frac{[\alpha]}{[\alpha]_F} = \frac{[\alpha]}{[\alpha]_S} = \frac{X_{S-H} - X_{R-H}}{X_{S-F} - X_{R-F}} = X_H = y$$

Therefore, in the perfect resolution, which is approached by the S-1 and S-3 Kinetic Batches at all temperatures studied, and by the S-2 and R-1 Kinetic Batches at 150°, the extent of transformation, y , equals $[\alpha]/[\alpha]_F$.

In the kinetic runs where $[\alpha]_F$ is far from $[\alpha]_S$ or $[\alpha]_R$, it may not be accurate to equate X_H and $[\alpha]/[\alpha]_F$. In these samples, (S-2 and R-1 from 105-135°) where nucleation of racemic material can occur to a considerable extent, situations can conceivably arise where X_H advances more rapidly than $[\alpha]/[\alpha]_F$. For example, extensive nucleation of racemic eutectic form occurring at the beginning of the transformation would not increase $[\alpha]/[\alpha]_F$ but would increase X_H . In kinetic runs where $[\alpha]_F \ll [\alpha]_S$, therefore, the extent to which X_H is approximated by measured rotations should be independently determined.

An independent measurement of X_H can be performed by following the resolution reaction by X-ray powder diffraction. We therefore monitored the resolution of the S-2 Kinetic Batch at 125° (Figure 19, p 105, kinetic run after four months at 0°) using quantitative X-ray powder photography. The method we used was similar to the "direct comparison method" described by Cullity.^{76a} By choosing one line in the diffraction pattern of the racemate ($d = 10.1 \text{ \AA}$) and one in the pattern of the eutectic form ($d = 6.4 \text{ \AA}$) which would be distinct in a mixture of the two forms, the disappearance of racemate and the appearance of eutectic could be quantitatively followed. A standard procedure for the development of the powder photographs was devised, so that when the developed photographs were analyzed on a microdensitometer, the resulting peak areas were reproducible. A calibration curve (Figure 23) relating the

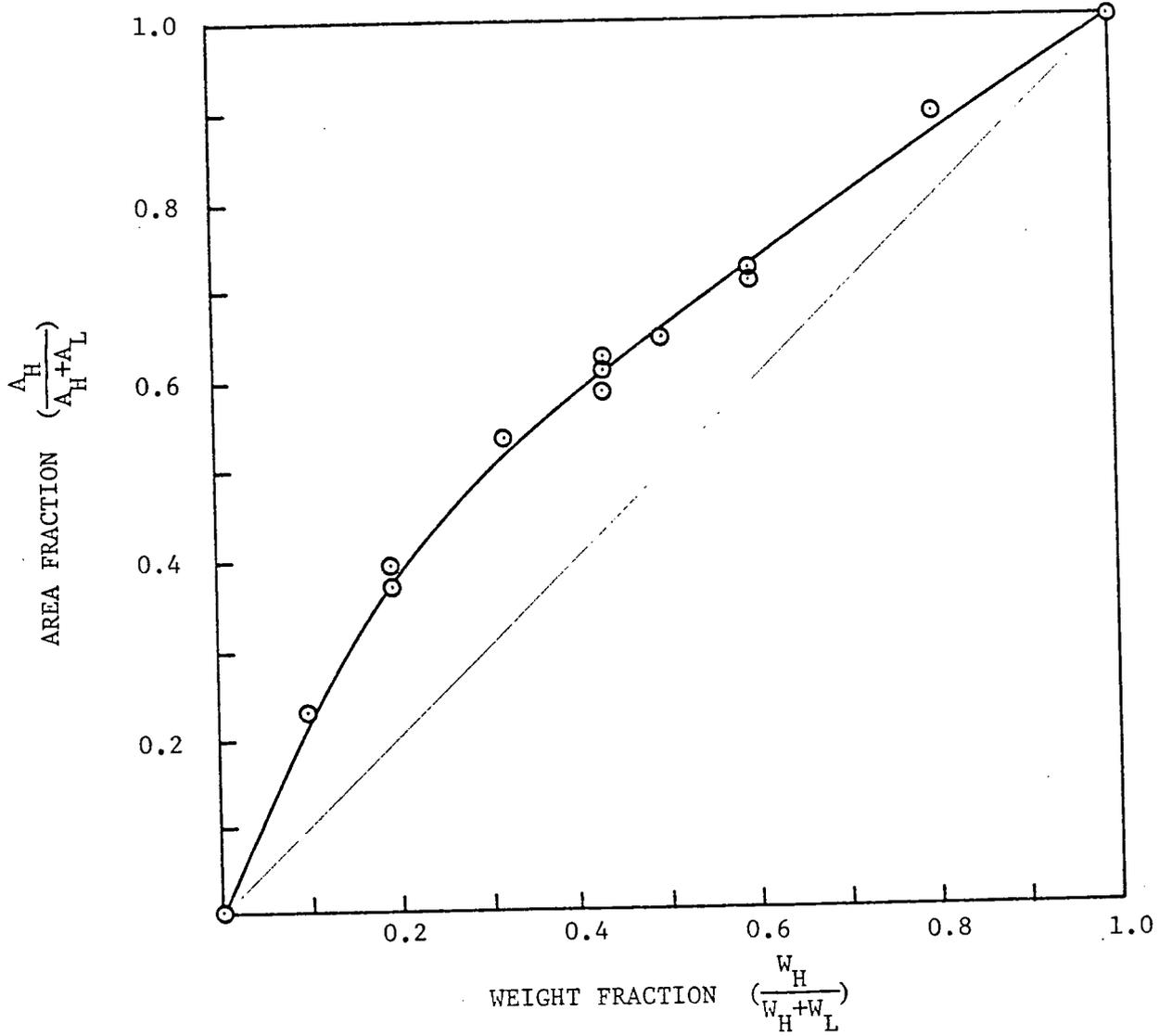


Figure 23. Calibration curve for quantitative phase analysis by X-ray powder photography.

peak "area fraction" of eutectic (high-melting) form (A_H/A_H+A_L) to the weight fraction of eutectic form (W_H/W_H+W_L) was constructed by analyzing known mixtures of the two forms. In several cases (e.g. at a weight fraction of 0.435) more than one sample was taken from the known phase mixture, to check the reproducibility of the method. These multiple analyses agreed to within 2%.

Samples of the S-2 Kinetic Batch were held at 125° for various lengths of time, then cooled to room temperature and analyzed for specific rotation as well as for phase content. The results are plotted in Figure 24, which shows how $[\alpha]/[\alpha]_F$ depends on X_H . The straight diagonal represents the case where $[\alpha]/[\alpha]_F = X_H$.

As shown by the results given in the Figure, the development of optical activity, even in samples of 1,1'-binaphthyl which do not resolve well, is rather closely paralleled by the phase change racemate \rightarrow eutectic form. The initial S-2 material contains some eutectic form, as expected from its initial activity of $[\alpha] = +11.8^\circ$. However, the extent of phase transformation is rather small considering the initial rotation, implying that the eutectic form in the sample is pure S. For if no R crystals were present, $X_H = X_{S-H}$ and from Equation 19, $X_H = X_{S-H} = [\alpha]/[\alpha]_S = 11.8/245 = 0.0482$. If R crystals existed in the initial sample, X_H would be even larger. This result verifies the conclusion in Section 3.5.1 that the S-2 sample resolves poorly because of nucleation of racemic material rather than the presence of R crystals in the initial sample.

To a good approximation, then, the extent of transformation is given by $[\alpha]/[\alpha]_F$. One would expect that the approximation would improve

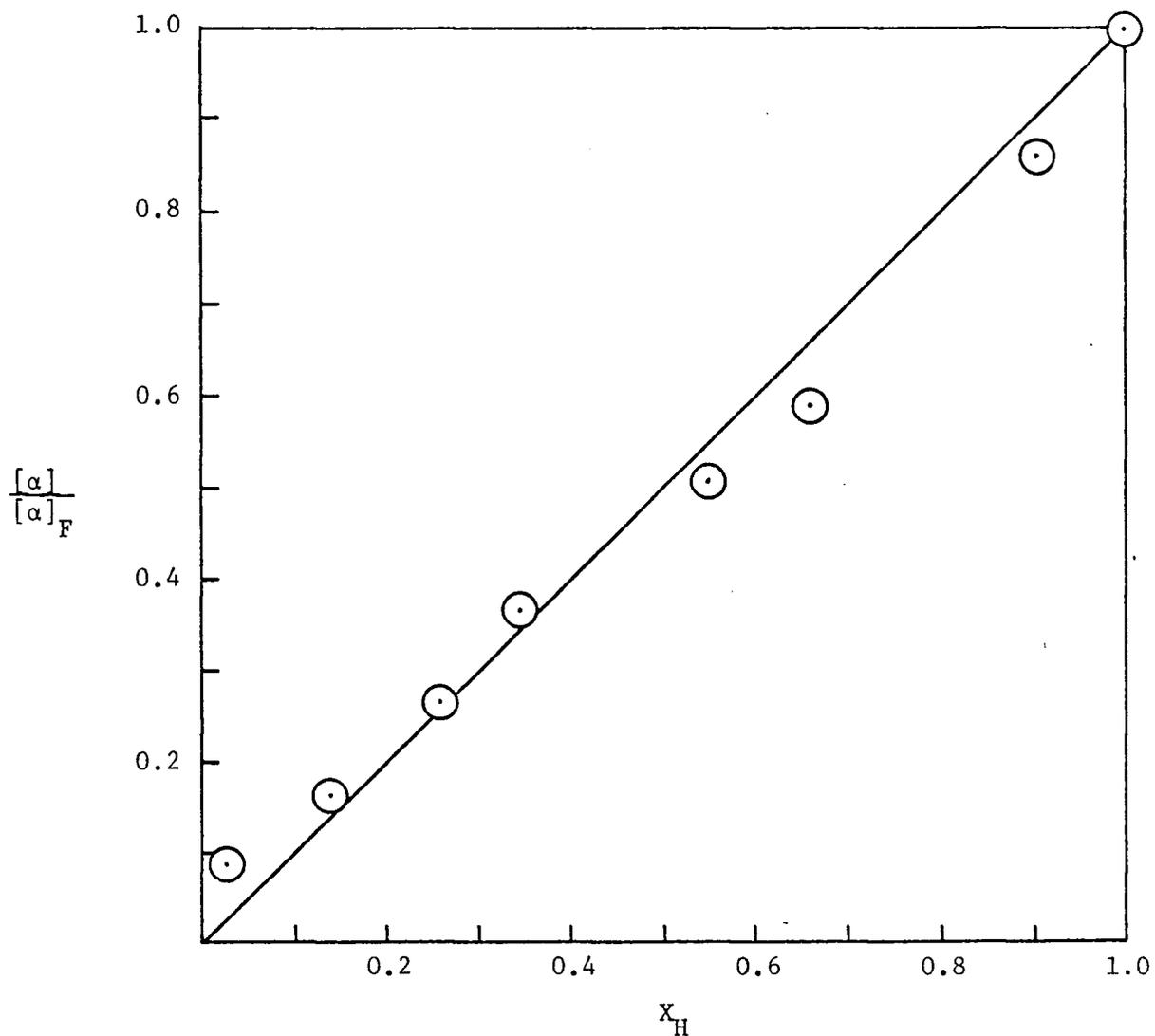


Figure 24. Development of specific rotation with extent of phase transformation (X_H), S-2 Kinetic Batch at 125° (after four months' storage at 0°). Diagonal represents the condition $[\alpha]/[\alpha]_F = X_H$

as $[\alpha]_F$ approached $[\alpha]_S$ (or $[\alpha]_R$), until in the perfect resolution, as discussed above, $[\alpha]/[\alpha]_F$ must equal X_H . With this assurance, an analysis of the kinetic results according to rate laws can now be conducted.

The kinetics of reactions in solids consisting initially of a single component have been considered in some detail in two major fields of research. The kinetics of phase transformations have received considerable interest in metallurgy,^{87,88} and the kinetic behaviour of decomposition reactions (more inorganic⁸⁹ than organic¹) has been explored rather widely in chemistry. However, from all of these investigations one must conclude that there exists no universal rate equation which describes the kinetics of all reactions in single solid components. The theoretical approaches to such solid-state reactions find illustration in a limited number of systems, and often describe only the initial or final part of a reaction.⁸⁹ On the other hand, empirical rate equations known to apply to a larger number of systems are difficult to interpret exactly in terms of reaction mechanisms.⁹⁰ The complexities of many solid-state reactions have even led to the development of methods of treating kinetic results in the absence of any assumed rate equation.^{88,91,92}

Of the empirical rate equations that have been developed,⁸⁸ two are most widely used. The first of these, usually called the Avrami-Erofeev Equation in inorganic chemistry^{90,93} or the Johnson-Mehl-Avrami Equation in metallurgy⁹² appears, in differential form, as:

$$[20] \quad \frac{dy}{dt} = k_6^n t^{n-1} (1-y)$$

and in integrated form, as:

$$[21] \quad y = 1 - \exp\left(-\frac{k_6^n}{n} t^n\right)$$

or:

$$[22] \quad \log \log\left(\frac{1}{1-y}\right) = n \log(t) + n \log(k_6) - \log(2.303 n)$$

Agreement with this rate expression will therefore be revealed by linearity of a plot of $\log \log\left(\frac{1}{1-y}\right)$ vs. $\log(t)$. Such an analysis was done for all four kinetic batches, two of which are illustrated in Figures 25 and 26.

The second commonly used rate law is the Prout-Tompkins Equation,^{89,90} which in differential form is:

$$[23] \quad \frac{dy}{dt} = k_7 y (1-y)$$

and which integrates to:

$$[24] \quad \log\left(\frac{y}{1-y}\right) = k_7 t + \text{constant}$$

The resolution kinetics of all batches were treated according to this equation, and some representative $\log\left(\frac{y}{1-y}\right)$ vs. time plots are shown in Figures 27 and 28.

In the recent accounts of solid-state reaction kinetics,^{58,90,93} it has been emphasized that caution should be used in interpreting any apparent fit of empirical results to solid-state rate equations. Kinetic

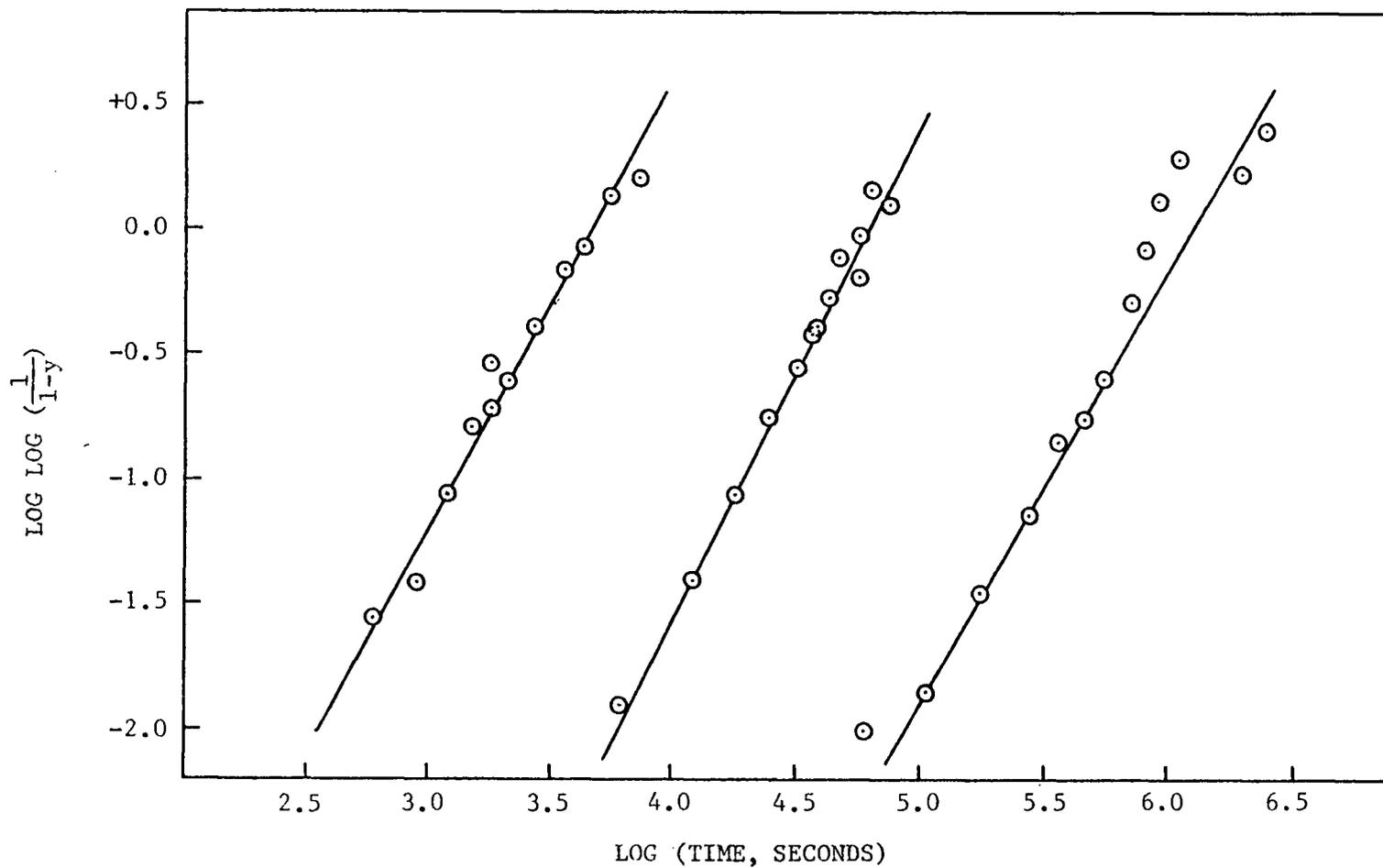


Figure 25. Avrami-Erofeev plots for the solid-state resolution of neat, polycrystalline, 1,1'-binaphthyl, S-1 Kinetic Batch at 135° and 105°. The sample stored six weeks at 25° is plotted against log (time, seconds) + 1.

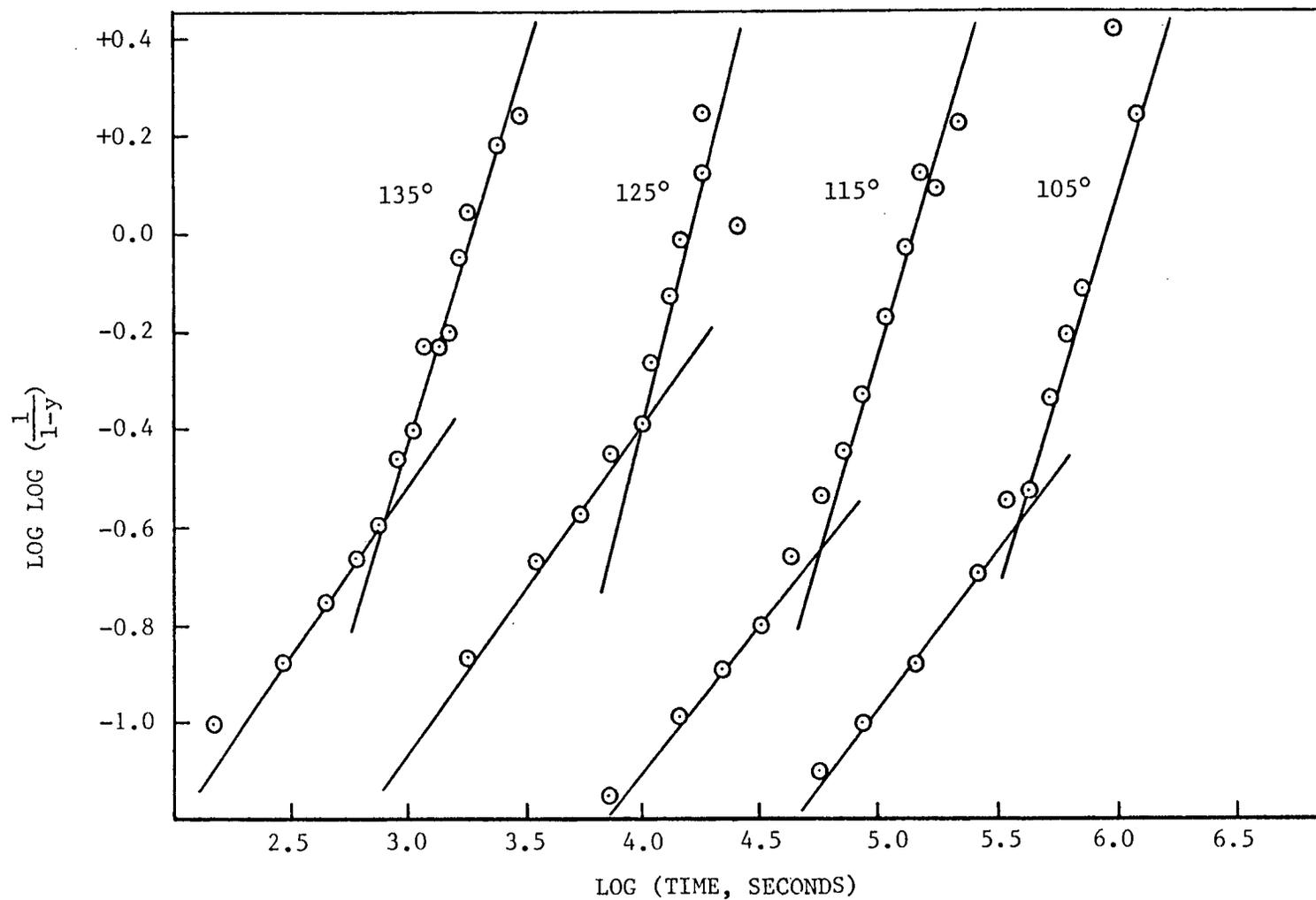


Figure 26. Avrami-Erofeev plots for the solid-state resolution of neat, polycrystalline 1,1'-binaphthyl, S-2 Kinetic Batch at 135°, 125° (original run), 115°, and 105°.

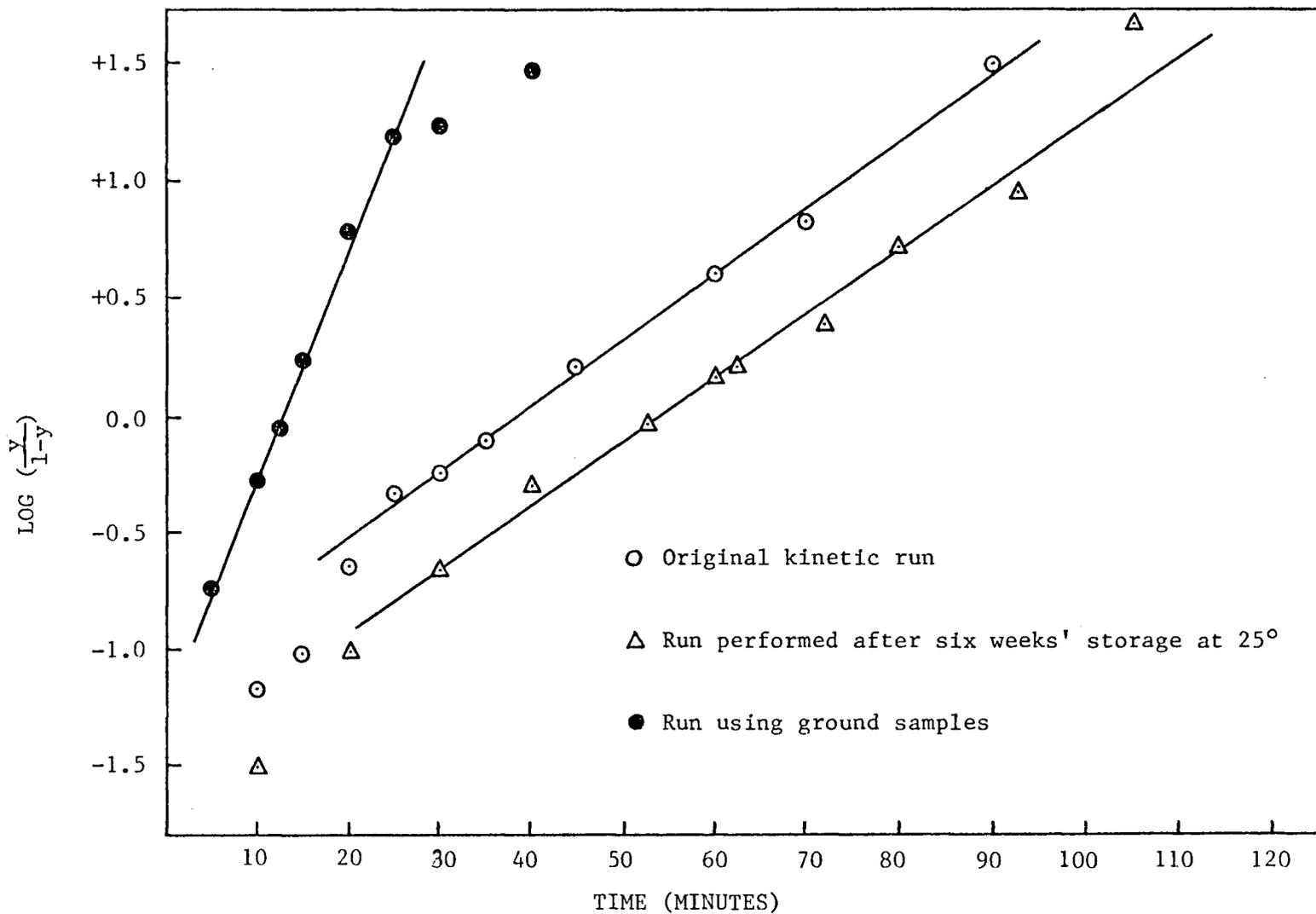


Figure 27. Prout-Tompkins plots for the solid-state resolution of neat, polycrystalline 1,1'-binaphthyl, S-1 Kinetic Batch at 135°. Effect of grinding and of storage at 25° for six weeks.

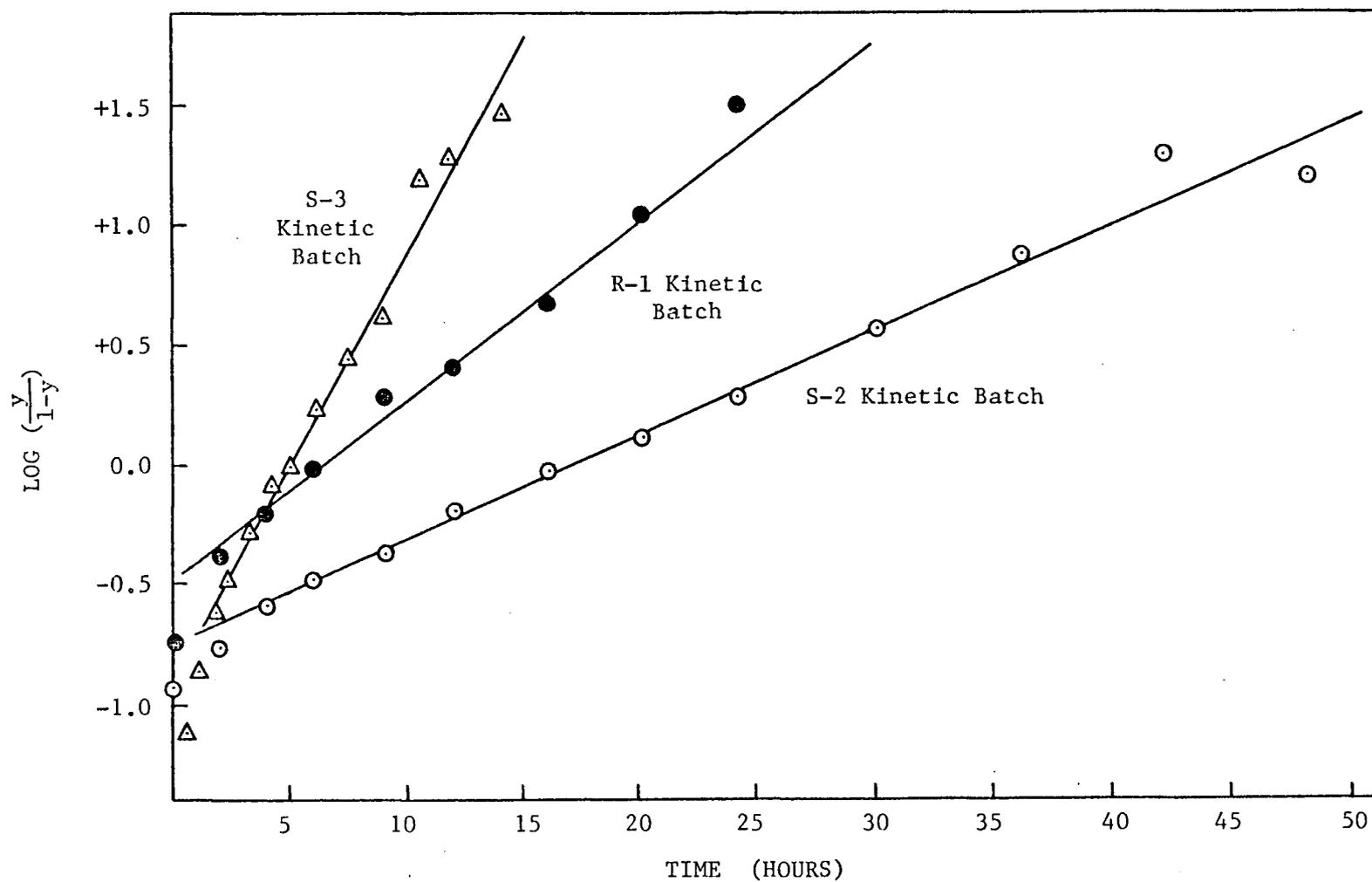


Figure 28. Prout-Tompkins plots for the solid-state resolution of neat, polycrystalline 1,1'-binaphthyl, S-2, S-3 and R-1 Kinetic Batches at 115°.

results should, wherever possible, be supplemented by additional information, such as the direct observation of the nucleation and growth processes under the microscope. Indeed, there are even cases of agreement with both the Avrami-Erofeev and Prout-Tompkins Equations,^{58,89} and in such cases recourse must be made to non-kinetic observations before any mechanism can be proposed. Even when the fit is poor when the entire reaction is considered there has been a tendency to look for straight portions over only part of the reaction^{21,89} (e.g., $y = 0.2$ to $y = 0.5$), the justification for this being that different mechanisms apply to different parts of the reaction. However, any meaningful analysis from such partial fits should be backed by many kinetic points known very precisely, as well as by additional observations.

No microscopic observations of the solid-state resolution of 1,1'-binaphthyl were made, so that any interpretation of the empirical plots must be considered as subject to verification by independent methods.

Let us consider first the Avrami-Erofeev plots (Figures 25 and 26). The slope of Equation 22 gives the exponent n (Table XIV). With the S-1 Kinetic Batch the results fit a straight line (with n near two) rather well. Less perfect fits are found with the S-3 and R-1 material (not shown), where the plot is better described at some temperatures by two straight lines (both slopes are listed in Table XIV). The most obvious bend occurs with the S-2 Kinetic Batch (Figure 26), which gives limiting slopes of ca. 0.65 and 1.7 at all four temperatures.

The straight line obtained with the S-1 material merits some discussion. The exact mechanistic implication of this fit is not altogether certain, considering that Equation 21 has been derived in a number

Table XIV

Avrami-Erofeev Exponents for the Solid-State Resolution of 1,1'-Binaphthyl

Kinetic Batch	Temperature, °C	Exponent
S-1	135.0	1.8
"	135.0 ^a	2.0
"	105.1	1.8
S-2	135.0	0.7 to 1.6 ^b
"	124.9	0.7 to 1.9 ^b
"	114.9	0.6 to 1.6 ^b
"	105.1	0.6 to 1.6 ^b
S-3	135.0	1.6
"	124.9	1.7
"	114.9	1.2 to 1.7 ^b
"	105.1	0.8 to 1.3 ^b
R-1	135.0	1.0 to 2.0
"	124.9	1.0
"	114.9	0.7
"	105.1	0.8

^a Run performed after six weeks' storage at 25°.

^b Minimum and maximum values.

of different ways.^{44b,90} One common interpretation^{58,90} of the exponent n is that it is composed of two quantities, namely, $n = \beta + \lambda$. The exponent β refers to the number of steps required to form a nucleus, and is revealed in a power law of the type $N = k t^\beta$, where N is the number of nuclei formed in time t . The number β is usually determined from the initial kinetics of a solid reaction or from counting the nuclei visible under a microscope as a function of time. However, as shown in Section 3.5.1 (p 103), the S-1 and S-3 Kinetic Batches do not undergo nucleation of new material, so that $\beta = 0$. The exponent λ is the number of dimensions in which growth of existing product crystallites occurs. Hence our observation of $n = \lambda = 2$ with the S-1 material can be taken as implying that the growing S crystallites spread in two dimensions along, for example, preferred lattice planes or boundaries between racemate crystallites.

Although lower values of n result from plots of the other kinetic batches, these have little significance in view of the rather poor fit. The S-2 Kinetic Batch (Figure 26) might suffer a change in mechanism partway through the reaction, but the kinetic points are too imprecise to justify such an interpretation.

The rate constant k_6 (Equations 20-22) has sometimes been evaluated from a plot of $[\log (\frac{1}{1-y})]^{1/n}$ against time, once n has been determined.⁵⁸ This procedure allows the determination of an activation energy, but there have been objections⁸⁸ to the comparison of such activation energies to those for other molecular processes. This objection is based on the fact that k_6 arises in a rate equation expressing dy/dt in terms of time as well as y (Equation 20), whereas

the most commonly encountered rate constant results from an expression of dy/dt as a function of y only.⁸⁸

The Prout-Tompkins plots (Figure 27-28) show linearity beyond $y \approx 0.3$ ($\log(\frac{1}{1-y}) \approx 0.37$) for all kinetic batches. Prout-Tompkins plots often show two straight lines, yielding rate constants which may or may not have the same activation energies.^{44b,58} In the 1,1'-binaphthyl case, there may be a second line of greater slope below $y = 0.3$, but there are far too few points in this region to verify this possibility.

The rate constants derived from the Prout-Tompkins plots are listed in Table XV. Since the constant k_7 is defined in terms of y only (Equation 23), an activation plot is worthwhile. Such a plot has been done in Figure 29. The Arrhenius activation energies, calculated from $2.303 R$ (slope of line), are 57.7, 62.5, 59.4 and 67.0 kcal mole⁻¹ for the S-1, S-2, S-3, and R-1 Kinetic Batches, respectively.

The theoretical basis for the Prout-Tompkins Equation lies in considering the reaction as proceeding by a branching process which spreads throughout the polycrystalline solid.⁹⁰ While the exact nature of the branching species is uncertain, one likely mechanism involves the spread of reaction product along grain boundaries, dislocations, and the like, causing the breaking apart of reactant crystallites and the creation of new avenues for the advance of the product.⁵⁸ Since in the case of the S-1 and S-3 Kinetic Batches, high resolutions were obtained, the chain branching process is most likely a growth process only and does not involve the nucleation of new material.

That growth is a branching process can be seen qualitatively from Equation 23. The rate of transformation depends both on the amount

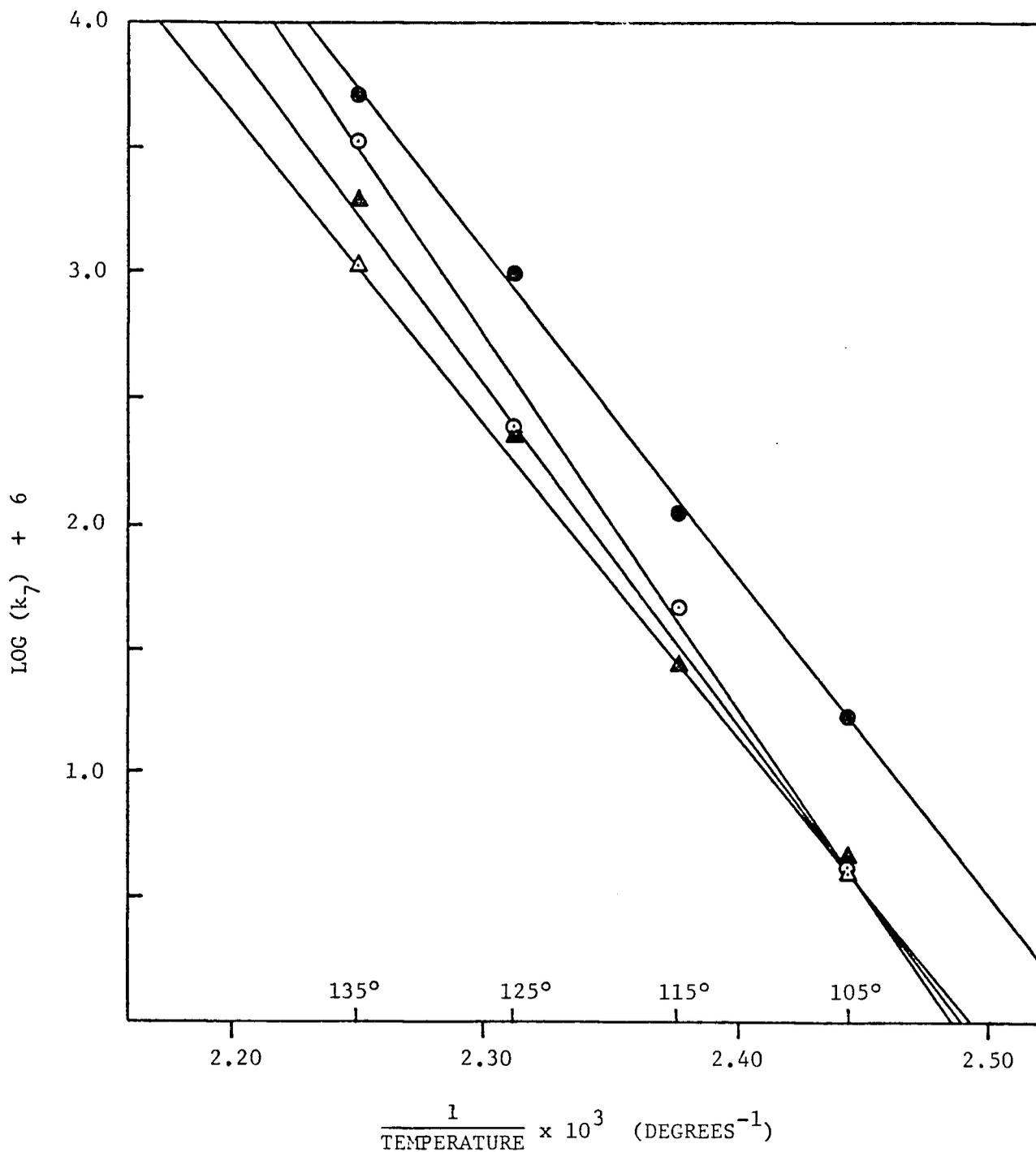


Figure 29. Relation of $\log(k_7)$ (from Prout-Tompkins plots) to reciprocal temperature for the solid-state resolution of neat, polycrystalline 1,1'-binaphthyl, all four kinetic batches. Straight lines are least squares fits to data for each batch.

Table XV
 Prout-Tompkins Rate Constants (k_7) for the Solid-State Resolution of
 1,1'-Binaphthyl

Kinetic Batch	Temperature, °C	$k_7 \times 10^5 \text{ sec}^{-1}$
S-1	135.0	107.6
"	135.0 ^a	103.6
"	135.0 ^b	377.1
"	105.1	0.4036
S-2	135.0	194.8
"	124.9	22.71
"	114.9	2.766
"	105.1	0.4638
S-3	135.0	514.3
"	124.9	100.8
"	114.9	11.45
"	105.1	1.733
R-1	135.0	340.7
"	124.9	25.11
"	114.9	4.782
"	105.1	0.4216

^a Run performed after six weeks' storage at 25°.

^b Run performed with ground samples.

of material transformed (y) and that which has not yet reacted ($1-y$). The rate equation is that of an autocatalytic reaction.^{44b,88} In order for a dependence on y , the product (crystals of pure enantiomer) must be available to the reactant (the racemate), a situation which is approached if the product is highly dispersed. This is in contrast to individual, compact spheres of growing product, which would isolate the reactant phase from much of the product.

Some attention should now be given to the rather large activation energy for the growth of crystals of pure enantiomer throughout the polycrystalline racemate. For the resolution to occur, 1,1'-binaphthyl molecules must be released from the racemate crystallites, interconvert in the reactant-product interface, then add to the growing product crystallites. The rate-determining step for the process cannot be simply the release of molecules from the racemate to an interface resembling the melt, since only some 7 kcal mole⁻¹ are required to melt the racemate (Section 3.3.2, p 75). More probably, the slowest step involves not only the release of 1,1'-binaphthyl from the racemate, but also the simultaneous interconversion of enantiomers. But the racemization of 1,1'-binaphthyl in *n*-heptane solution requires only 21.7 kcal mole⁻¹ activation energy,⁶⁶ a figure which, when added to 7 kcal mole⁻¹, is still far from the observed 62 kcal mole⁻¹.

The largest possible energy increment associated with the removal of molecules from a molecular crystal is the heat of sublimation, also called the binding energy, of the crystal. Binding energies for aromatic hydrocarbons are usually of the order of 20 kcal mole⁻¹ (anthracene is "fairly typical" at 22 kcal mole⁻¹).⁹⁴ However, the energy (per molecule) required to remove a single molecule from inside a crystal to the vapour

is twice the energy (per molecule) needed to vaporize the entire crystal, since twice as many Van der Waals bonds are broken in the former case.^P Doubling the binding energy and adding the 21.7 kcal mole⁻¹ required for enantiomer interconversion is much closer to the activation energy of 62 kcal mole⁻¹.

For 1,1'-binaphthyl, the heat of sublimation of the crystal can be estimated as follows. With nonpolar molecules, the heat of vaporization of the melt is related empirically to the normal boiling point through Trouton's rule:⁹⁵

$$\frac{\Delta H_{\text{vaporization}}}{T_{\text{b.p.}}} = 21 \text{ cal deg}^{-1} \text{ mole}^{-1}$$

The boiling point of 1,1'-binaphthyl has been determined⁹⁶ as 240° at a pressure of 13 torr, which converts to a boiling point of 410°C (638°K) at atmospheric pressure, using a common vapour pressure-temperature nomograph.⁹⁷ The heat of vaporization is therefore 14.3 kcal mole⁻¹. If $\Delta H_{\text{vaporization}}$ is the same at 105-135°C as it is at 410°C (probably a crude approximation), and if ΔH_{fusion} is the same in this temperature range as at 145°C, then:

$$\Delta H_{\text{sublimation}} = \Delta H_{\text{fusion}} + \Delta H_{\text{vaporization}}$$

^P If the coordination number of the crystal is n , then there are $n/2$ bonds per molecule in the crystal, i.e., vaporizing the entire crystal breaks $n/2$ bonds per molecule. However, if a single molecule is removed, all n bonds to it must be broken. Therefore, twice the energy per molecule is required.

from 105–135°C and at atmospheric pressure. Therefore, $\Delta H_{\text{sublimation}}$ for the low-melting (racemate) form is $14.3 + 7.3 = 21.6 \text{ kcal mole}^{-1}$. The energy required to remove one 1,1'-binaphthyl molecule to infinity (effectively, 2 \AA) is therefore $43.2 \text{ kcal mole}^{-1}$, and if the molecule must simultaneously interconvert, the activation energy could be as high as $43.2 + 21.7 = 64.9 \text{ kcal mole}^{-1}$.

Such a high activation energy represents an upper limit to the simple breaking of Van der Waals forces in the racemate crystal accompanied by the conformational flip which interconverts enantiomers. The fact that 1,1'-binaphthyl seems to require almost all of this energy to reach the transition state means that the molecule needs considerable freedom to interconvert in the reactant-product interface. The entropy of activation would have to be quite favourable in order for the reaction to be observable at all. Therefore, both with the resolution of 1,1'-binaphthyl and the racemization of the (+)-diacid 29 in the solid phase, a high activation energy is observed and is compensated by a high activation entropy, facilitating the solid-state reactions.

In summary, we should emphasize that although some high degree of control can be exercised over the solid-state resolution of 1,1'-binaphthyl, each prepared batch remains an individual. The kinetic complexities of such interface-controlled solid-state reactions should not, however, overshadow the significant fact that reactions in organic solids can occur with facility and with fascinating stereochemical consequences.

3.6 The Spontaneous Generation of Optically Active 1,1'-Binaphthyl^{98,99}

In this section are described some experiments involving the crystallization of 1,1'-binaphthyl from the melt in a closed system. These experiments grew out of our earlier attempts (Section 3.4.2, p 91) to obtain, reproducibly, 1,1'-binaphthyl of high specific rotation by seeding the supercooled melt in open test tubes. A few preliminary crystallizations in sealed ampules in which optically active seeds were purposefully excluded had shown that optical activity could develop even in a closed system consisting initially of a racemic 1,1'-binaphthyl melt. Both enantiomers could be obtained. It then became of interest, as a separate problem, to examine the behaviour of a large number of individual sealed samples, keeping a tally of the direction and magnitude of the specific rotations obtained.

Accordingly, two hundred individual ampules containing about 20 mg of carefully weighed 1,1'-binaphthyl crystals (from various racemic batch preparations) were sealed and then held, in groups of twelve, at temperatures of 170 to 185° for five minutes to melt and destroy all forms of solid 1,1'-binaphthyl. The totally melted samples were then quickly transferred to a bath maintained at 150°. At this temperature the melt will remain supercooled almost indefinitely. Crystallization was induced, however, by removing each sample, holding it against a piece of Dry Ice for a few seconds, then quickly replacing it in the 150° bath. In this manner, a small area of the bulk of the melt was cooled drastically, forming some seed crystals on which the remaining melt could crystallize at 150°. Crystallization was complete within three hours. The solid samples were then cooled to room temperature,

opened, and analyzed for optical activity. The material obtained was almost always optically active, although excessive application of the cooling Dry Ice resulted in no activity. These few cases of specific rotations less than $\pm 2^\circ$ were not considered in the following statistical analysis.

The distribution of the 200 specific rotations is shown in Figure 30, which is a presentation of percentage of observations falling within various rotations. The largest observed rotations of the 200 were $[\alpha] = -218^\circ$ and $+206^\circ$ (optically pure 1,1'-binaphthyl (Appendix A, p 178) is $[\alpha] = \pm 245^\circ$); however, as shown, samples of low rotation ($\pm 2^\circ$ to $\pm 48^\circ$) were most common. The observed rotations fit a Gaussian distribution with a mean of $[\alpha] = +0.14^\circ$ and a standard deviation of 86.4° .^q From this distribution it is apparent that obtaining 1,1'-binaphthyl with an optical purity above 90% by this method would be a very exceptional event (observable about once in 150 tries).

The symmetry of the distribution is reflected in Figure 31 by the ratio of the number of S-(+) samples to the total number of samples plotted for two runs of 100 samples each. As the total number of samples increases, the ratio tends toward 0.5 and it falls at all points well within the 99% confidence limits calculated for a probability of 50% (+) and 50% (-) samples. After 200 independent crystallizations, the number of dextrorotatory samples obtained (95) is insignificantly different from the number of levorotatory samples obtained (105).

^q If the cases of $[\alpha] = 0^\circ$ obtained from overcooling the samples were included in this treatment, the symmetry of the distribution would, of course, be preserved, but the standard deviation would be reduced.

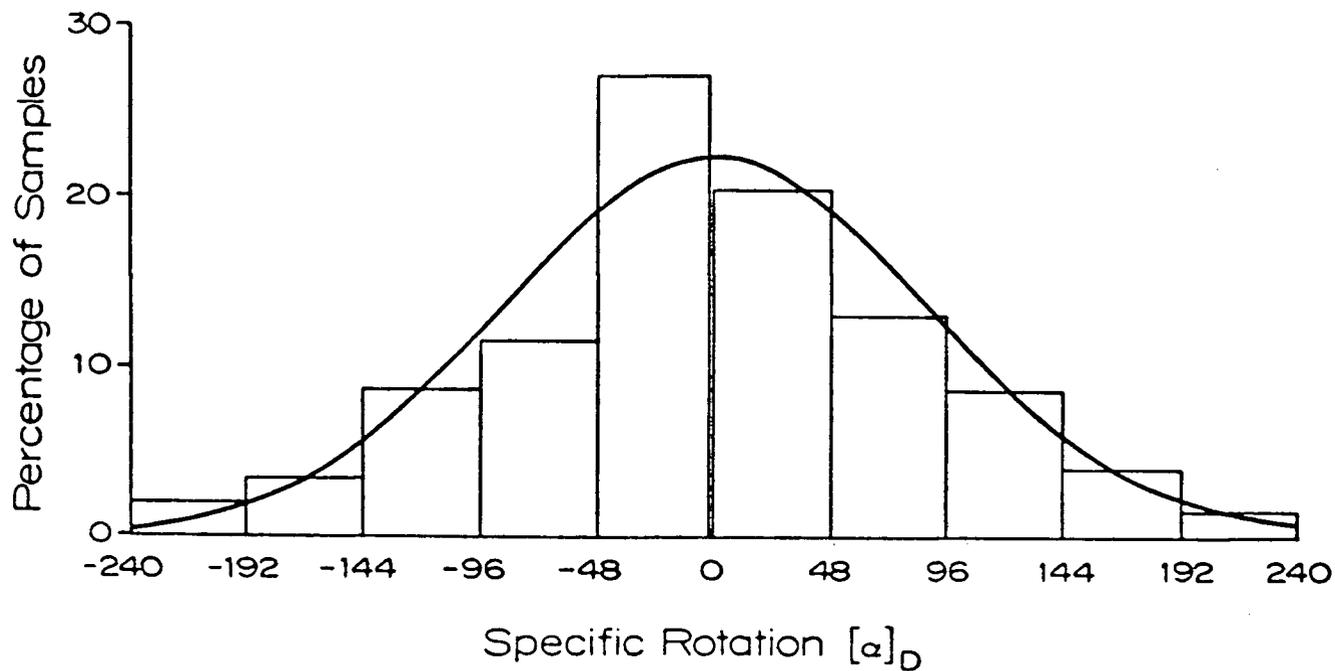


Figure 30. Percentage of 1,1'-binaphthyl samples giving specific rotations between $\pm 240^\circ$. The curve shows the Gaussian normal distribution calculated for the mean of $+0.14^\circ$ and standard deviation of 86.4° .

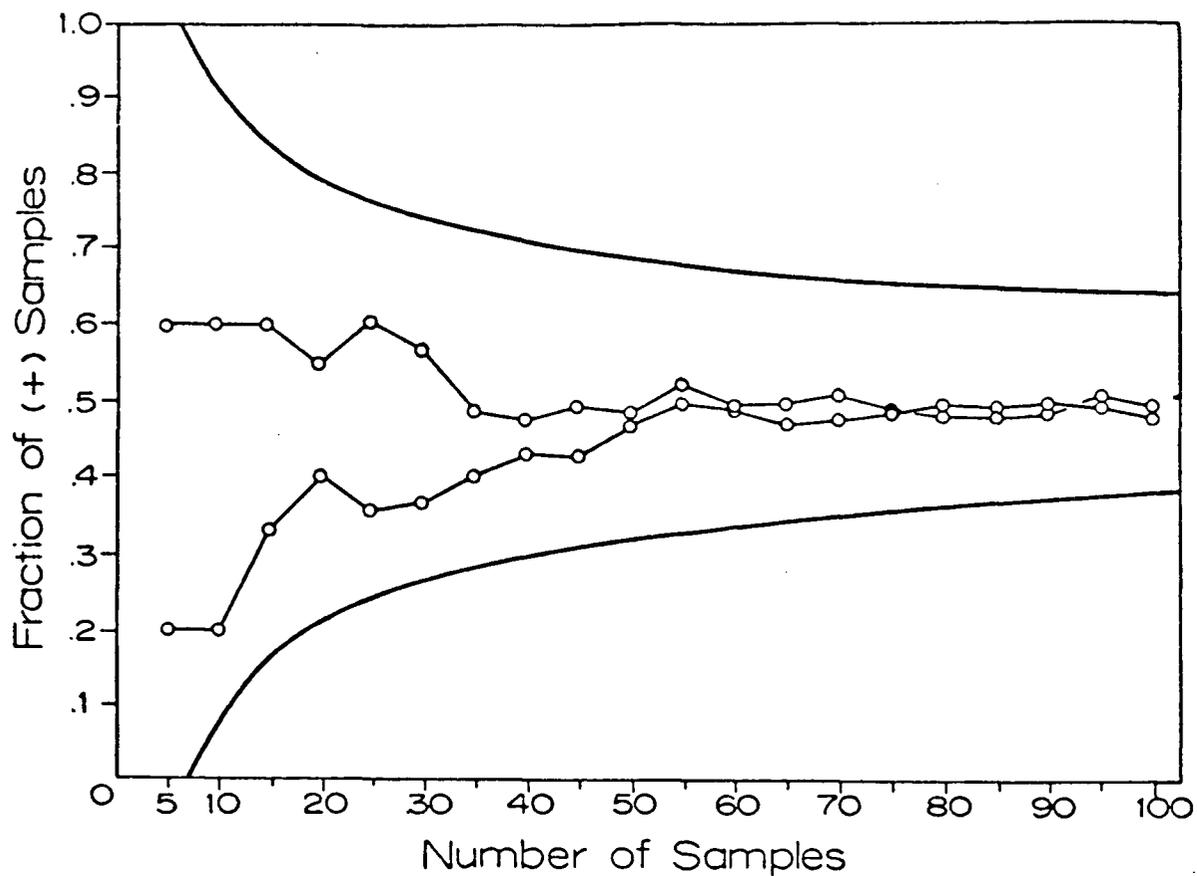


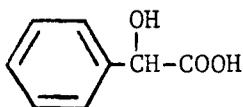
Figure 31. Ratio of samples having positive rotations to the total number of samples of 1,1'-binaphthyl crystallized at 150°. The 200 samples are treated as two sets of 100 each. The curves are confidence limits calculated for a 0.99 degree of confidence and a probability of 50% positive and 50% negative for each sample.

An important conclusion can be drawn from the symmetric probability distribution. The development of optical activity in each sample was determined by only the chance formation of R or S crystals from the racemic melt. The generation of optical activity in the 1,1'-binaphthyl system is truly spontaneous. Here, "spontaneous" is taken as meaning "pertaining only to the system itself." A spontaneous resolution, therefore, occurs when measurable optical activity is produced from a totally racemic system in the complete absence of external dissymmetric influences of any type - physical, chemical, or human. The probability distribution of a large number of individual resolutions is a sensitive check for the presence of any such external influence, which will be revealed as a mean specific rotation significantly different from zero, and as a greater number of samples of one handedness than the other, as shown by an approach to the 99% limits of confidence calculated for the totally random situation.

Although the spontaneous generation of optical isomers in a totally symmetric environment seems intuitively reasonable, it has never before been carefully demonstrated.⁹⁸ In fact, quite the opposite has been observed. The reported examples of attempts to eliminate all dissymmetric influences from several systems, which are recently reviewed^{98,99} have shown a tendency for preferential crystallization of one enantiomorph. This may simply be a reflection on the small number of individual trials in some investigations (after 10 samples, even 1,1'-binaphthyl showed eight negative and two positive rotations), but nevertheless, such apparent bias has engendered the feeling that the totally symmetric experiment is either extremely difficult because of omnipresent optically active impurities¹⁰⁰ or completely impossible because of a weak dissym-

metric bias in the universe.¹⁰¹ The fact that 1,1'-binaphthyl is capable of truly spontaneous resolution not only proves that such a phenomenon is possible, but also that dissymmetric materials which were almost certainly present as dust particles or less well defined dissymmetric forces, do not always influence the development of optical activity. Perhaps one could say that because 1,1'-binaphthyl is a relatively unnatural compound, its nucleation and crystallization is insensitive to dissymmetric impurities derived from life.

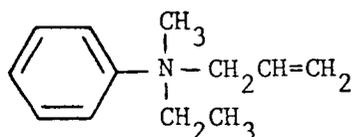
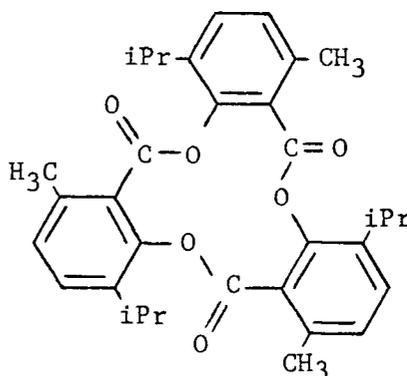
The question therefore arises as to which, if any, dissymmetric materials can influence the 1,1'-binaphthyl resolution. We therefore performed several individual crystallizations in the presence of both d- and l-mandelic acid (37). The addition of 5% by weight of d-mandelic



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acid in experiments at 130° similar to those described above produced 1,1'-binaphthyl with an excess (+) rotation (after correcting for the small rotation arising from mandelic acid) in 18 out of 19 samples. On the other hand, 5% l-mandelic acid in 1,1'-binaphthyl gave samples with (-) rotations in 17 tries out of 17. These distributions fall well outside those calculated for a 50-50 probability and they indicate that the configuration of mandelic acid essentially completely controls the configuration of 1,1'-binaphthyl obtained.

It is possible to distinguish three types of systems in which spontaneous resolution is possible. The first, exemplified by R- and S-1,1'-binaphthyl, is a system in which crystallization can occur from a racemic liquid containing rapidly interconverting enantiomers. The presence of a mechanism for interconversion means that the system finishes crystallizing in a thermodynamically stable state. The final product can therefore be analyzed at leisure for any optical activity (provided, of course, that interconversion is slow enough at room temperature to permit analysis). Other examples, involving crystallization from solution rather than from the melt, are the systems (+)- and (-)-methylethylallylanilinium iodide (38)¹⁰² and (+)- and (-)-tri-*o*-thymotide (39)¹⁰³. Although these systems develop optical activity

3839

from a racemic solution, the number of samples taken in each is too few to decide whether dissymmetric impurities are influencing the resolution, i.e., whether or not the resolution is truly spontaneous.

The second type of system in which it might be possible to demonstrate spontaneous resolution is one in which enantiomers are optically stable, but a solution (or melt) is only partially crystallized. In

such a system, total crystallization would, of course, lead to a racemic batch of crystals. In a partial crystallization, the crystals could well have an excess of one enantiomer while the liquid phase contains an excess of the other. However, this represents an unstable state, since the liquid phase will always be supersaturated in one enantiomer, and the two phases must be successfully separated (by filtration) without disturbing the metastable liquid. In spite of the seemingly precarious procedure, this method is rather widely used,⁸⁵ to resolve enantiomers under non-spontaneous conditions (e.g. the purposeful addition of seed crystals).

The third system which can in principle show spontaneous resolution is one which contains an achiral molecule in solution (or in the melt). If such a compound crystallizes in an enantiomorphous space group, then an excess of molecules in one enantiomorphous crystal constitutes, in a sense, a resolution of optically active crystals. As with the first type of system, the final state is thermodynamically stable. However, analysis presents some problems, since in an individual crop of crystals each must be weighed and examined for hemihedral faces or optical rotation, before it can be concluded that the given crop contained an excess of molecules in one enantiomorphous crystal. Sufficient crops must also be examined before any conclusions as to spontaneity can be drawn. In spite of this time-consuming requirement, Soret¹⁰⁴ examined 844 crystallizations of sodium chlorate from solution in sealed ampules, and observed an excess of right-handed crystals in 51.3% of the samples, while 48.7% of the samples had left-handed crystals in excess. Other results¹⁰⁵ record a weighted average of 50.08 dextrorotatory crystals

from 46 independent crops. As far as we know, this is the only other carefully demonstrated case of the spontaneous generation of optically active material.

Unlike the enantiomorphous sodium chlorate crystal, which loses all optical activity immediately on dissolution, the 1,1'-binaphthyl system involves the spontaneous creation of optically active molecules which retain their configuration for a considerable length of time in solution (at 0°). The resolution of 1,1'-binaphthyl is therefore a simple illustration of Calvin's hypothetical scheme¹⁰⁶ for the autocatalytic selection of one enantiomer in the genesis of optically active molecules.

3.7 Conclusion

The development of optical activity simply by heating and cooling a racemic material like 1,1'-binaphthyl seems, at first thought, to be an impossible process. The thought arises because the interconversion of enantiomers in solution always leads to racemization, not resolution, because of an increase in entropy due to greater disorder. But in going from such a homogeneous system to a heterogeneous system such as the phases formed between two enantiomers, resolution can become a possible, even probable, process.

Resolution is compatible with the achievement of lower free energy because enthalpy and entropy changes accompanying phase transformations can more than compensate for any losses in free energy due to formation of molecules of only one kind. These losses are, in fact, very small. For example, even the most intimate of mixtures of enantiomers - the liquid solution of one in the other - would lose only $1.37 \text{ cal deg}^{-1} \text{ mole}^{-1}$

of entropy and no enthalpy (in the case of ideal solutions) in hypothetically changing from a racemic to a fully resolved state.⁴⁶ At 150°, this entropy change amounts to 580 cal mole⁻¹ of free energy. The entropy difference between the far less intimate mixture found in a eutectic conglomeration of large aggregates (crystallites) of pure enantiomers and the polycrystalline single enantiomer is even smaller. In fact, the entropy, enthalpy and free energy of mixing are implicitly taken as zero when two pure solids form a mechanical mixture and the free energy of the mixture is linearly related to its composition.⁵¹ Therefore, there is little, if any, thermodynamic preference for the formation of a racemic eutectic mixture over that of a polycrystalline single enantiomer.

The choice of which is formed is governed entirely by kinetics. In the spontaneous crystallization of 1,1'-binaphthyl from the melt, the chance formation of one enantiomer lowers the free energy of activation towards the further crystallization of that enantiomer by presenting a surface on which molecules of only one configuration may be deposited. The element of chance can be completely eliminated by performing a controlled solid-state resolution through the preparation of a highly stereospecific solid consisting of a racemate and seed crystals of the desired enantiomer.

The R- and S-1,1'-binaphthyl system illustrates the novelty of working with the phase transformations of optically labile enantiomers. A sample of neat 1,1'-binaphthyl ($[\alpha] = +234^\circ$) held at 160° racemizes completely in less than five minutes. Another sample of low optical activity ($[\alpha] = +11^\circ$) can be prepared so that it will resolve to

$[\alpha] = +214^\circ$ in less than five minutes at 150° , only 10° lower in temperature.

How general is this phenomenon? The development of optical activity by crystallization of the melt requires that the enantiomers interconvert relatively quickly in the melt and yet be optically stable (unlike the (+)-diacid 29, Section 2) as a eutectic mixture. The controlled solid-state resolution requires the existence of two racemic modifications, either a racemate or a solid solution which decomposes to a eutectic mixture at temperatures where interconversion is relatively rapid.

The existence of more than one crystalline modification of a single compound is more widespread than commonly supposed. Over one-third of all organic compounds studied thermodynamically up to 1969 exhibit polymorphism.^{107a} It is the opinion of several authors^{81a} that every organic compound possesses more than one solid state, which have only to be discovered through suitably oriented research.

The unprecedented solid-state resolution of 1,1'-binaphthyl, although surprising when first encountered, is actually easily explained and should be anticipated in future studies with phase systems of optical isomers.

4. EXPERIMENTAL

4.1 General

Reagents and solvents used were reagent grade and were employed without further purification, unless otherwise noted. Melting points, determined on a Thomas Hoover Capillary Melting Point apparatus in unsealed capillaries, were corrected. Infrared spectra (all nujol mulls) were run on a Perkin-Elmer 137 sodium chloride spectrophotometer. Analytical procedures requiring a more detailed description (polarimetry, differential scanning calorimetry, and X-ray powder diffraction) are described in Section 4.6.

4.2 Preparations

4.2.1 Preparation of Racemic Naphthidine (31)

The procedure followed for the preparation of racemic naphthidine was similar to that of Cohen and Oesper.⁷⁰ In a 1 l beaker, 27.9 g of pulverized α -naphthylamine were stirred into 500 ml water, 33.8 ml of concentrated hydrochloric acid was added, and the mixture warmed on a steam bath to give a light purple precipitate of α -naphthylamine hydrochloride. The mixture was then cooled in an ice bath to 0-3° and cold, diluted sulfuric acid (21 ml of the concentrated acid plus 200 ml water) was stirred in. The suspended amine salt was then diazotized (with vigorous stirring, keeping the temperature near 0°) by

slowly adding a cold solution of 14 g sodium nitrite dissolved in 90 ml water. The reddish brown solution of the diazonium salt was allowed to stand for 5 min in the ice bath then suction filtered, the filtrate being received in a precooled filter flask surrounded by an ice bath. The cold filtrate was transferred to a 2 l beaker (ice bath) and a cold solution of 79.9 g anhydrous potassium acetate in 300 ml water was slowly stirred in, the temperature being kept below 4°. A cooled solution of 31 g sodium sulfite in 200 ml water was then slowly added, causing a vigorous evolution of nitrogen and the appearance of 1,1'-azonaphthalene crystals. After the addition of sodium sulfite solution was completed the solution was allowed to stir for an additional 5 min. The suspension was then taken out of the ice bath, warmed on a steam bath to ~60°, and the orange precipitate was filtered off, washed with water, and dried in air.

Without further purification the crude azonaphthalene (ca. 18 g) was pulverized and suspended in 200 ml 95% ethanol, and brought to a weak boil. A solution of 48 g stannous chloride dihydrate in 100 ml concentrated hydrochloric acid was slowly added over ca. 5 min (with occasional swirling). A colour change (from yellow to reddish-brown) occurred, and the mixture was immediately cooled to room temperature. Concentrated hydrochloric acid (100 ml) was then added to precipitate any remaining naphthidine hydrochloride. The precipitate was washed with water, then suspended in 200 ml water. Twenty ml of 20% sodium hydroxide was then added, and the mixture allowed to stir at 40° for 10 min. The slurry was cooled in an ice bath, filtered, washed with water and dried in air. The crude naphthidine was dissolved in 160 ml

of a hot 3:1 ethanol-pyridine solvent pair. The hot solution was filtered and allowed to cool slowly. The purified naphthidine (7.1 g, 26% from α -naphthylamine) was obtained as well-formed, light brown plates (m.p. 201-202°, lit.⁷⁰ 198-199°).

4.2.2 Preparation of (+)-Naphthidine- α -bromo- $\underline{\underline{D}}$ -camphor- π -sulfonate (33)

This salt was prepared using the procedure of Theilacker and Hopp.⁷¹ To 400 ml water and 40 ml 1 N hydrochloric acid was added a solution of 2.84 g (10 mmoles) racemic naphthidine in 50 ml hot acetone. This was followed immediately with 6.54 g (20 mmoles) (+)-ammonium- α -bromo- $\underline{\underline{D}}$ -camphor- π -sulfonate. A light-brown precipitate soon formed and the mixture was allowed to stand at room temperature overnight. The precipitate was filtered and recrystallized from 70 ml 60% (by volume) ethanol-water. Two crops (4.27 g, 46%) were obtained. This material gave a specific rotation of $[\alpha]_D^{25} = +80^\circ$ (lit.⁷¹ $[\alpha]_D^{20} = +99^\circ$).

4.2.3 Preparation of S-(+)-1,1'-Binaphthyl from 33

The salt 33 was directly deaminated to S-(+)-1,1'-binaphthyl using a procedure similar to that of Colter and Clemens.⁶⁵ To an ice-cold suspension of 150 ml water, 3.45 g of salt 33, 2.3 ml concentrated hydrochloric acid, and 50 ml 50% hypophosphorous acid in a 3-necked flask fitted with an overhead stirrer was added 1.2 g sodium nitrite. After 2 h an additional 1 g sodium nitrite was added to the cold mixture and stirring was continued for another 3 h. The flask was then stoppered lightly and placed in the refrigerator overnight (0°).

For two days the flask was stirred and kept cold during the daytime and stored in the refrigerator overnight, during which time a total of 6 g sodium nitrite were added in 1 g portions.

The cold mixture was filtered and the solid material suspended in 200 ml cold (8°) benzene. The suspension was filtered and the solution extracted successively with 10% sodium hydroxide, water, 10% hydrochloric acid, and water (all at ~ 8°), and dried over anhydrous MgSO₄. After filtration (cold apparatus), the benzene was removed on the rotary evaporator (25-30°), and the solid placed on a column (with a water jacket) packed with 25 g alumina (Woelm, neutral, activity grade 1) in petroleum ether (30-60°). Cold water was circulated through the jacket. The fractions, eluted with 4% (by volume) benzene-petroleum ether (30-60°) afforded white crystals (0.536 g, 55%) of optically active 1,1'-binaphthyl ($[\alpha]_D^{25} = +97^\circ$; m.p. 156-157°; lit.⁶⁵ $[\alpha]_D = +145-192^\circ$, m.p. 156-159°; lit.⁶⁴ $[\alpha]_{5791} = +245^\circ$, m.p. 157-159°).

4.2.4 Preparation of Racemic 1,1'-Binaphthyl

The procedure used was analogous to that of Sakellarios and Kryimis.⁷² To a dry 3-necked flask fitted with an overhead stirrer and condenser was added (under dry nitrogen) 9.6 g magnesium turnings, 72 ml anhydrous ether, 56 ml α -bromonaphthalene and a single crystal of iodine. The stirred mixture was heated to reflux to start the reaction, which proceeded without further heating for 20 min. The reaction mixture was then heated to reflux for 6 h, with the addition of up to 200 ml dry benzene to thin the slurry when necessary. The reaction was cooled to room temperature and added slowly to a stirred suspension of 54 g

anhydrous cupric chloride (prepared by drying the dihydrate salt for 4 h at 100°) in 200 ml anhydrous ether. The ensuing vigorous reaction was controlled with an ice-water bath. The suspension was then stirred overnight at room temperature under dry nitrogen.

The reaction mixture was quenched by slow addition to 100 ml 10% hydrochloric acid and ice. The ether-benzene layer was extracted successively with several portions of 10% hydrochloric acid, water, saturated sodium bicarbonate solution and water, and dried over anhydrous magnesium sulfate. The solvents were removed in vacuo to afford an oil, which crystallized on cooling to 0°. The brown material was transferred to a Buchner funnel, washed with a small amount of cold petroleum ether (30-60°), and recrystallized once from petroleum ether (65-110°). The crude 1,1'-binaphthyl (~ 12 g) was then mixed with an equal weight of alumina (Shawinigan reagent) and placed on a column of 300 g alumina packed in petroleum ether (30-60°). After 1 ℓ had been eluted with 10% benzene-petroleum ether (30-60°), the first appearance of 1,1'-binaphthyl was revealed by the presence of white crystals at the tip of the column. The entire binaphthyl fraction required 3 ℓ for complete elution. Evaporation of the solvent in vacuo and recrystallization of the binaphthyl from acetone afforded 10 g (20%) of white crystals, m.p.'s 144-145° (low-melting form) and 157-158° (high-melting form). Badar, et al.⁷³ report m.p. 144.5-145° (low-melting form) and 157-159° (high-melting form).

4.3 Procedures for the Resolution of Racemic 1,1'-Binaphthyl

4.3.1 Resolution in Completely Melted Samples

4.3.1.1 Spontaneous Resolution

To observe resolution from a melt which is totally racemic, carefully weighed samples of 1,1'-binaphthyl (from several different batch preparations) ranging from 10-30 mg in weight were sealed in 1 ml glass ampules. In groups of 12, the sealed ampules were held in a silicone-oil at 170-185° to destroy all forms of solid 1,1'-binaphthyl. The completely melted samples were then quickly transferred to a second silicone oil bath maintained at precisely 149.6°, where they would have remained as a supercooled melt indefinitely. Crystallization was induced by removing the ampules individually from the bath, holding each one against a piece of Dry Ice for ca. 5 sec, then immediately replacing it in the 149.6° bath. The cooling operation was performed quickly, so that no sample was outside of the bath for more than 10 sec. The samples required about 2 h to crystallize completely, after which time they were cooled to room temperature, opened, and analyzed for optical activity.

Polycrystalline 1,1'-binaphthyl containing a known amount of a dissymmetric "impurity" (d- and l-mandelic acid) was prepared as follows. In 50 ml acetone (distilled from potassium permanganate) 0.49252 g racemic 1,1'-binaphthyl and 0.02639 g d-mandelic acid were dissolved. The solution was filtered and the solvent removed in vacuo. The resulting mixture, which contained 5.08% (by weight) d-mandelic acid, was sealed in ampules, melted, and crystallized in a manner analogous to the above procedure with the completely racemic 1,1'-binaphthyl. A similar procedure was used for the mixing of l-mandelic

acid with racemic 1,1'-binaphthyl.

4.3.1.2 Deliberate Addition of Crystals of Active 1,1'-Binaphthyl

To test the effect of optically active 1,1'-binaphthyl seed crystals on crystallization from completely melted samples (Table XI, p 93), ca. 200 mg of solid racemic 1,1'-binaphthyl (from various batch preparations) were placed in the bottom of a test tube 15 cm in length and fitted with a ground glass stopper. The solid was introduced through a long-stemmed funnel to avoid coating the upper part of the test tube with crystals. The entire tube (except for the top 2 cm) was then immersed in a bath at 170-180°, where all 1,1'-binaphthyl melted, and immediately transferred to a 149.6° bath and immersed to the same level. The stopper was removed for ca. 10 sec while the active 1,1'-binaphthyl seeds were dropped in from the tip of a spatula. Crystallization required overnight (16 h) to become complete. The sample was then cooled to room temperature, the cake of solid broken up with a spatula, and duplicate analyses for optical activity performed.

4.3.2 Resolution in the Solid State

4.3.2.1 The Heating of Racemic 1,1'-Binaphthyl

As a standard characterization of freshly prepared racemic 1,1'-binaphthyl, a few individual samples from a given batch of racemic material were heated at 149.6°. Samples were cooled to room temperature and analyzed for optical activity (Table III, p 51 and Table VIII, p 85).

In some experiments (Table X, p 92) carefully weighed optically active binaphthyl was added to the weighed racemic material before the ampules were sealed. The sealed samples were then mixed thoroughly by holding them in contact with a Lab-Line "Super-Mixer" for 5 min, heated at 149.6° and analyzed for specific rotation.

4.3.2.2 Cycling Solid 1,1'-Binaphthyl to High Specific Rotation

At the bottom of a 15 cm test tube was placed 2.00 g of racemic 1,1'-binaphthyl (Racemic Batch G). The test tube was sealed, placed in a 149.6° bath for 2 h (the sample appeared to remain solid throughout), then cooled to room temperature and opened. Polarimetric analysis gave $[\alpha]_D = +42^{\circ}$. The solid was dissolved in 400 ml pentane, and the solution was filtered, boiled down to 150 ml allowed to cool to room temperature (total time at the b.p. of pentane (36°) was 15-20 min), and placed in the refrigerator (0°) for 1 h. The pentane was removed on the rotary evaporator to afford 94% material having the same specific rotation ($[\alpha]_D = +43^{\circ}$). The 1,1'-binaphthyl was then sealed in a second test tube and heated, as before, at 149.6° for 2 h. The recrystallization from pentane was repeated in exactly the same manner as before, preparing the material for the third heating at 149.6° . The cycle was repeated a fourth time to obtain 1.10 g (the weight losses due mainly to samples taken for polarimetric and differential scanning analyses) of S-(+)-1,1'-binaphthyl, $[\alpha]_D = +194^{\circ}$. Other cycling experiments (Table IV, p 54) were patterned after the above procedure.

4.3.2.3 The Heating of Slightly Active 1,1'-Binaphthyl

(a) The Preparation of S-1 Kinetic Batch

A solution of 0.181 g of active 1,1'-binaphthyl ($[\alpha]_D = +208^\circ$) and 3.819 g of racemic 1,1'-binaphthyl (comprising together 4.000 g of material with $[\alpha]_D = +9.4^\circ$) in 280 ml acetone (Fisher reagent) was prepared and filtered into a 500 ml Erlenmeyer flask. The solution was then placed in a Dry-Ice-acetone bath, with occasional swirling. Precipitation, which began in ~ 10 min, appeared to be complete in 1 h. The crystals were suction filtered immediately on removal from the cold bath. The 1,1'-binaphthyl obtained (2.97 g, 74% recovery) possessed a specific rotation of $[\alpha]_D = +1.4^\circ$. Samples taken from this batch resolved to $[\alpha]_D = +211^\circ$ within 16 h at 149.6° . Other batches prepared by this procedure did not always resolve well on heating.

(b) The Recrystallization-Evaporation Procedure - The Preparation of S-3 Kinetic Batch

A solution of 0.133 g of active 1,1'-binaphthyl and 5.57 g of racemic 1,1'-binaphthyl (comprising together 5.70 g of material with $[\alpha]_D = +2.2^\circ$) in 400 ml acetone (freshly distilled from potassium permanganate) was filtered into a 1 l round-bottom flask. The solution was then cooled in a Dry Ice-acetone bath (-78°) for 10 min with swirling, during which time crystallization began. Without completing the crystallization, the flask was removed and immediately placed on a rotary evaporator (Buchi Rotavapor <R>). The flask was rotated in air while full vacuum (water aspirator) was being established (5 min), then was lowered into the water bath, maintained between 20 and 25° . As the

flask warmed, some (but not all) of the crystals dissolved, then reprecipitated with the loss of solvent. The evaporation was taken to dryness, and any residual acetone was removed on the high vacuum pump. The material, which was 100% recovered, possessed an activity of $(\alpha) = +2.0^\circ$, and resolved to $(\alpha) > +200^\circ$ on heating at any temperature between 105° and 150° .

Kinetic batches S-2 and R-1 were prepared by an analogous procedure. The solid 1,1'-binaphthyl ($[\alpha]_D = \pm 2^\circ$ to $\pm 15^\circ$) obtained by this method almost always resolved to at least $[\alpha]_D = \pm 190^\circ$ on heating to 150° for 2 h.

4.3.3 Resolution Involving Optically Inactive Solvents

4.3.3.1 Heating of Racemic 1,1'-Binaphthyl Under a Solvent

A glass tube 20 cm in length and containing a coarse fritted disc 10 cm from either end was held in a vertical position while 200 mg racemic 1,1'-binaphthyl was placed on the disc. The top end was then sealed, the tube inverted, and 0.5 ml 2-propanol (freshly distilled from stannous chloride) placed through the remaining open end. The sealed end was immersed in a dry ice-acetone bath to pull the 2-propanol through the disc and into the binaphthyl chamber. The open end was then sealed, and the entire tube submerged in a bath maintained at 120° , and oriented so that the binaphthyl/2-propanol mixture remained at the bottom end. About half the solid binaphthyl dissolved. After 43 h the tube was inverted in the bath, allowing the 2-propanol to drain from the 1,1'-binaphthyl through the fritted disc. Residual 2-propanol was removed by taking the tube from the bath and quickly immersing the 2-propanol chamber in Dry Ice-acetone.

This procedure allows complete removal of the solution from the crystals at 120°. Then binaphthyl end was then opened and the crystals were analyzed for optical activity. In this example, $[\alpha]_D = +198^\circ$, but such a high rotation was not consistently obtained (see Table IX, p 90).

4.3.3.2 Seeding of a Racemic, Supersaturated Solution

Using a procedure identical to the above (Section 4.3.3.1), 200 mg racemic 1,1'-binaphthyl and 0.5 ml isopropanol (freshly distilled) were placed in the sealed end of the fritted disc tube. In the open end was placed a glass capillary containing some seed crystals of active binaphthyl ($[\alpha] = -212^\circ$) at the tip remote from the fritted disc. The open end was then sealed and the tube immersed in a 135° bath. All of the binaphthyl in contact with the isopropanol dissolved. The tube was transferred to a 120° bath and inverted. The isopropanol solution of binaphthyl drained through the fritted disc and came in contact with the active seed crystals. After 20 h at 120°, some crystals had grown from the supersaturated solution, and the tube was again inverted to drain the solution from the crystals. The crystals were recovered as before, and analysis gave $[\alpha]_D = -2.3^\circ$. Seeding from solution, even with considerable care, did not consistently give highly-resolved 1,1'-binaphthyl.

4.4 Characterization of the R- and S-1,1'-Binaphthyl Phase System

4.4.1 The Crystal Picking Experiment

The batch of large (2-4 mm) crystals obtained by slow recrystallization (2 days) from actone solution was examined under a microscope

with permanently crossed polarizer and analyser and rotatable stage. Crystals which were not members of clumps were examined closely. Any small crystals adhering to the surface were removed, and if the entire crystal, viewed at any angle except normal to the c or d faces (Figure 10, p 62) extinguished sharply as the stage was rotated, it was set aside for polarimetric analysis. No attempt was made to polish the crystal faces, a few of which were rough in appearance.

4.4.2 Crystallization of Low and High-Melting Forms

In a typical recrystallization from pentane, 0.50 g of racemic 1,1'-binaphthyl was dissolved in 100 ml boiling pentane. The warm solution was filtered and the filtrate reduced to 40 ml by boiling off the pentane. The solution was either allowed to cool slowly to 0°, cooled rapidly in an ice bath, or seeded with various samples of racemic binaphthyl. Racemic Batches A to J were prepared by various recrystallizations from pentane (except D, which was prepared by recrystallizing 0.50 g racemic 1,1'-binaphthyl from 10 ml glacial acetic acid). Racemic Batches K, L, and N were prepared by recrystallization from petroleum ether (65-110°), using 25 ml solvent for each gram to be recrystallized. Racemic Batch M was recrystallized from acetone at -78° (see Section 4.4.3 for a similar procedure), and Racemic Batch O was a commercial sample of 1,1'-binaphthyl (K and K Laboratories, Inc.).

To check for the crystal modifications of 1,1'-binaphthyl produced by slow and fast removal of solvent, 100 mg portions of racemic material were dissolved in 15 ml solvent (ether, acetone, or benzene).

Slow evaporation: The solutions were filtered into three 25 ml Erlenmeyer flasks and placed under an upturned beaker for several days. The ether solvent disappeared within one day, the acetone in two days, and the benzene in four days. Fast evaporation: The three solutions (prepared as above) were not filtered, but were subjected to a stream of dry air while being held in a water bath at room temperature. Solvents were removed within 5 min. The crystals from all six samples were analyzed on the d.s.c.

Slow and fast solidification of the racemic melt was studied on the d.s.c. (Section 4.6.2). Solid racemic 1,1'-binaphthyl was melted in a d.s.c. sample planchette at 160°, then cooled at a rate of 20 deg min⁻¹ to obtain pure low-melting form. A fresh sample (or the same one) was melted at 160° and cooled rapidly by removing the sample planchette and placing it on a metal surface. Replacing the sample in the d.s.c. and warming to 90-100° gave pure high-melting form. The most sudden cooling of the melt was obtained by packing a capillary for X-ray powder diffraction (Section 4.6.3) with racemic 1,1'-binaphthyl melting the sample at 175°, and immediately immersing the (unsealed) capillary in a liquid nitrogen bath. The capillary was retrieved and mounted in a Debye-Scherrer camera for analysis.

4.4.3 Phase Limit of Resolution

The following procedure used for R-(-)-1,1'-binaphthyl was similarly applied to S-(+)-1,1'-binaphthyl. In 180 ml acetone (distilled from potassium permanganate) was dissolved 1.53 g of R-1,1'-binaphthyl ($[\alpha]_D = -216^\circ$). The solution was filtered and immersed

in a Dry Ice-acetone bath (-78°). The length of time at room temperature was 15 min. Crystallization was complete after 30 min at -78° (occasional swirling). The crystals were then rapidly suction-filtered through a sintered glass funnel. Both crystals (1.26 g, 82%) and material from solution were analyzed for optical activity, the latter made possible by removal of acetone solvent in vacuo at 25° within 15 min. The recrystallized R-1,1'-binaphthyl possessed $[\alpha]_{\text{D}} = +228^{\circ}$, the material from solution having $[\alpha]_{\text{D}} = -111^{\circ}$. Three further recrystallizations were performed, with the results listed in Table XVI, p 179.

4.5 Kinetic Methods

4.5.1 Standard Procedure

The procedure for the kinetic study of the racemization of the diacid 29 in the solid and the melted states, was identical with that of the solid-state resolution of 1,1'-binaphthyl. In both cases, 10-30 mg of the neat, polycrystalline material was carefully weighed in 1 ml ampules. The ampules were sealed in air, and completely immersed in a constant-temperature silicone oil bath. At appropriate times individual samples were withdrawn, cooled to room temperature, opened, and analyzed for optical activity.

For the solution phase racemization of (+)-29, sealed ampules contained ~ 10 mg of carefully weighed (+)-29 and 0.2 ml purified tetralin. The diacid 29 dissolved only when the samples were heated for the run; concentrated solutions (ca. 0.27 M) were therefore possible.

First-order rate constants (k_{obs}) were obtained by plotting $\log ([\alpha]/[\alpha]_0) + 2$ against time, where $[\alpha]_0$ is the specific rotation (sodium D line) at time zero. The rate constant was calculated from $k_{\text{obs}} = 2.303 \times (\text{slope of line})$.

4.5.2 Kinetic Runs with 1,1'-Binaphthyl from 64° to 98°

Samples of 1,1'-binaphthyl were sealed in the standard way and placed in a drying pistol with a jacket for refluxing solvents. Temperatures were maintained by the following solvents: 64.2°, methanol; 76.9°, carbon tetrachloride; 83.3°, 1,2-dichloroethane; 87.6°, 1:3 tetrachloroethylene-water; 93.0°, 1:3 1-butanol-water; and 97.7°, n-heptane. Activities obtained at these temperatures are listed in Table XIII, p 111.

4.5.3 Kinetic Runs with Ground Samples

Samples of 1,1'-binaphthyl were ground in a small (1 cm o.d.) test tube using a glass stirring rod which had been molded to fit the bottom of the test tube. This method was more satisfactory than pulverization in a mortar and pestle, which caused the buildup of a static charge on the crystals and made the handling of large (100 mg) quantities difficult.

4.5.4 Product Studies

In the racemization of (+)-29, samples remained colourless and crystalline throughout the runs at 130-155°. In the melt (176-194°) some yellowing occurred, but did not become significant before

racemization was complete. At 161 and 166°, yellowing was more apparent than in the melt, and the samples partially melted.

Racemic diacid 29 was heated in tetralin at 140° for 96 h (greater than 15 half-lives for racemization of (+)-29). Extraction of the diacid into 10% sodium hydroxide and acidification give racemic 29, whose nuclear magnetic resonance spectrum was identical with that of the original diacid. No fumaric acid signal was present in the spectrum. In another run, 0.45 g of the racemic diacid 29 was heated with 10 ml of tetralin at 140° for 52 h (ca. 9 half-lives). On cooling, 0.32 g (71%) of racemic 29, m.p. 180-184° was recovered. Extraction of mother liquors with dilute base gave 0.094 g (21%) of sticky, probably polymeric, solid. Essentially complete interconversion of enantiomers occurs before side reactions become important at long reaction times.

The kinetic batches of 1,1'-binaphthyl remained white, crystalline solids from 105-150° until well beyond completion of the resolution. At 98°, some yellowing occurred at long reaction times (3-6 months). The product of the resolution gives the d.s.c., infrared, and X-ray analyses of the high-melting form of 1,1'-binaphthyl (infrared spectra reported by Badar, et al.⁷³). Co-injection of the starting material and resolved product into a gas-liquid chromatograph [using an 8% SE-30 on Chromosorb W (80/100) (6 feet x 1/8 inch) column; carrier gas: helium; flow rate: 110 ml min⁻¹; temperature: 150° for 3 min, the heating at 32 deg min⁻¹ to 270°, maintained for 10 min; instrument: Perkin-Elmer 900 Gas Chromatograph] gave a single peak.

4.6 Analytical Procedures

4.6.1 Polarimetry

A Bendix type 143 A automatic polarimeter was used with a modified sample cell. The supplied cell holder assembly was used to contain a cell composed of a round metal spacer having a concentric hole and a thickness of 1 cm. Cell windows were composed of round glass slides separated from the spacer and the rest of the assembly by round Teflon wafers with holes punched in the center. The pieces of the cell were sandwiched together in the cell holder assembly in the intended fashion. Sample solutions were introduced through a hole drilled in the side of the metal spacer which formed the cell.

Each sample ampule (1 ml) from the kinetic runs was opened and the solid material completely dissolved in acetone (for the (+)-diacid 29, which does not racemize appreciably in acetone at 25°) or in benzene (for optically active 1,1'-binaphthyl, which possesses a half-life of 11.4 h for racemization in benzene at 25°⁷⁴). The solution was transferred to a 3 ml volumetric flask and diluted to the mark with washings from the opened ampule. Three readings were made by filling the polarimeter cell successively with three samplings (ca. 0.8 ml each) of the solution. Zero readings were taken using the pure solvent. All measurements were made at the sodium D line (5890 Å), and specific rotations were calculated from $[\alpha]_D = 3 \times 10^4 \times \alpha \times c /$ (sample wt. in mg) where α is the observed rotation and $c = 0.80$ is a cell constant obtained by calibration with known standard sucrose solutions.

4.6.2 Differential Scanning Calorimetry

The differential scanning calorimeter (d.s.c.) used was a Perkin-Elmer DSC-1B. For qualitative runs, ca. 5 mg crystals were placed in an aluminum sample planchette and covered with an aluminum lid. The lid was pressed firmly against the planchette, partially crushing the crystals, but the planchette and lid were not crimped together. A standard programming rate of 10 deg min⁻¹ was used unless otherwise noted. The temperature readout was carefully calibrated for 10 deg min⁻¹ heating rate with melting point standards, using slope settings of 545-585, and differential and average temperature settings of 485 and 522, respectively. Transition temperatures were measured at the beginning (i.e., at first departure from baseline) of recorded peaks.

For quantitative enthalpy determinations, the sample was weighed on a Cahn Electrobalance (Model M-10) and run through the transition on the d.s.c. at a programming rate of 10 deg min⁻¹, a range of 16x and a chart speed of 4 in min⁻¹ (Leeds Northrup Speedomax W chart recorder). A calibration run using the weighed high-purity indium standard provided was performed under identical conditions, from which it was learned that at the settings used, each square inch of chart paper represented a heat flow of 27.3 millicalories.^r Peak areas were integrated by taking the average of six determinations with a planimeter (Gelman Instrument Co.). The enthalpy of the transition in kcal mole⁻¹ was

^r The calibration factor changes somewhat with temperature,⁴⁷ but the value of 27.3 mcal in⁻² will not change significantly in the temperature range 140-190°.

calculated from:

$$\Delta H = \frac{(\text{area of sample transition, in}^2)}{(\text{weight of sample, mg})} \times (\text{molecular weight of sample}) \times 27.3 \times 10^{-3}$$

The heat capacity (C_p) measurements (Table XVII, p 190) were performed using the Specific Heat Kit, an accessory to the DSC-1B. The method involved comparison to a standard, which was a disc of high-purity sapphire. The sapphire standard was weighed, placed in a sample planchette, and covered in the recommended⁴⁷ manner. The d.s.c. was run isothermally to establish a baseline, then it was programmed at 10 deg min^{-1} (range: 4x), causing a pen deflection proportional to the heat capacity of the sapphire. The programming was discontinued after heating for ten degrees, and the baseline re-established. In this manner, the sapphire was heated from 50° to 150° in ten degree intervals which overlapped so that two measurements of the amplitude of the deflection could be made at 60°, 70°, ... 140°. The sapphire was removed and a blank run was performed with the same planchette in an identical fashion. The planchette was then filled with a weighed amount of 1,1'-binaphthyl (pure high-melting form) and the procedure repeated. All three (sapphire, blank and sample) runs were repeated with pure low-melting binaphthyl, from 50° to 140°. In neither sample did any weight loss or phase transformation occur. At each temperature the amplitude of the blank was subtracted from that of the sapphire and binaphthyl samples, and C_p (in $\text{cal deg}^{-1} \text{mole}^{-1}$) calculated from:

$$C_p = \frac{(\text{amplitude sample})}{(\text{amplitude sapphire})} \times \frac{(\text{weight sapphire})}{(\text{weight sample})} \times (C_p \text{ of sapphire, cal g}^{-1}) \times$$

$$(\text{molecular weight of 1,1'-binaphthyl})$$

The two sapphire runs agreed (in amplitude) to within 1% at all temperatures, good evidence of the precision of the method. The accuracy of the method was tested by measuring the heat capacity of naphthalene at 51° and 61° as 43.7 and 46.0 cal mole⁻¹deg⁻¹, respectively (lit.¹⁰⁸ 44.0 and 45.9 cal mole⁻¹deg⁻¹, respectively). The accuracy was better than 1%.

4.6.3 X-Ray Powder Diffraction

The following procedure for quantitative phase analysis was adopted. The sample to be analyzed was thoroughly pulverized in a small agate mortar, and packed firmly in a 0.3 mm glass capillary by placing the capillary in a test tube and holding the assembly against a Lab-Line "Super Mixer". The bottom 1.5 cm of the capillary was broken off, and aligned in a Debye-Scherrer powder camera (Philips PW 1024/10) equipped with the smaller (0.5 mm) collimator and beam stop. The camera was then loaded with Kodak No-Screen NS-392 T 35 mm X-ray film and mounted on the non-divergent quarter of the Philips PW 1008/85 X-ray generator (CuK_α radiation, Ni filter). The source was activated (40 kV and 15 mA, and the film exposed for exactly 20 h.

The film was developed with Kodak D-19 developer (a stock solution prepared as recommended, but using distilled water and bubbling nitrogen through the solution) diluted ten times with water at 20°C (68°F).

Development, performed in an Anscomatic 35 mm developing tank, took 4 min with swirling every 30 sec. The film was then immersed in a stop bath (stock solution: 13 ml glacial acetic acid in 1 l water), rinsed, and fixed (Kodak Rapid Fix, freshly prepared) for four minutes. After rinsing for 30 min, the film was immersed in Photoflow and hung to dry for 3-4 h.

The density of the diffraction lines on the photograph was measured on a Joyce double beam recording microdensitometer (mk III C). The following settings were used. Mode: Forward Integrate; differential control: 5; pen damping: 5; iris: fully open; slit height: full height; slit: 25; aperture: 25; density wedges: 0-2 optical density (O.D.) units (D 453) and 0-1 O.D. units (B 335); ratio arm: 10 times. The zero of optical density was taken as the density of unexposed, undeveloped film which had been fixed. The range of optical density (from the background fog level to the most dense measured peak) was measured with the 0-2 O.D. density wedge. In all films taken, this range was between 0.40 and 1.20 O.D. units (the linear range (where O.D. is proportional to exposure) of Kodak No-Screen film is 0.2 to 1.5¹⁰⁹). The diffraction lines to be measured were traced as peaks using the (more precise) 0-1 O.D. density wedge.

The diffraction lines chosen for intensity measurement were the 10.1 Å line of the racemate and the 6.4 Å line of the eutectic form. Integrated intensities were measured from the densitometer tracings using the average of six area determinations with the planimeter. The area of the eutectic (high-melting) form (A_H) was expressed as a fraction of the total area of the two peaks:

$$\text{area fraction (high-melting form)} = \frac{A_H}{A_H + A_L}$$

Calibration samples consisting of known weights of low- and high-melting forms were prepared by grinding and thoroughly mixing the two forms together, then analyzing these samples using the described X-ray procedure. The resulting weight fractions:

$$\text{weight fraction (high-melting form)} = \frac{W_H}{W_H + W_L}$$

were plotted against their corresponding area fractions (Figure 23, p 121) and the resulting calibration curve used to determine the phase content of samples of the S-2 Kinetic Batch at various stages of resolution (Figure 24, p 123).

The d spacings of the low- and high-melting forms (Table V, p 58) were calculated by measuring the diffraction lines on the photograph with an accurate millimeter scale, and converting to 2θ . This conversion was easy since the Philips camera was constructed so that 1 mm represented $2^\circ 2\theta$, allowing for "normal film shrinkage" on development. The d spacings were then obtained from the 2θ values and the relation:

$$d = \frac{\lambda}{2\sin\theta}$$

where λ is the wavelength of CuK_α radiation (1.5418 \AA). The intensities of the lines were obtained by integrating the peaks obtained from the microdensitometer.

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APPENDIX A

THE PHASE LIMIT OF RESOLUTION

Since all of our experiments with 1,1'-binaphthyl produced samples having various specific rotations, it was very desirable to know the highest possible rotation (at the sodium D line, where all of our specific rotations were measured) observable in the R- and S-1,1'-binaphthyl system.

An indication as to how this might be accomplished was obtained when several samples of highly active 1,1'-binaphthyl were recrystallized from acetone at -78° , as a final purification measure before the further study of samples with high activity. The material obtained from the recrystallization possessed a specific rotation higher than that of the original solid.

A study of the ternary system formed between R and S-1,1'-binaphthyl and an optically inactive solvent revealed that simply from phase equilibrium considerations alone, a highly resolved material should increase in specific rotation until a constant figure is obtained (see below). We therefore performed multiple recrystallizations on a sample of well-resolved R-1,1'-binaphthyl to see how high an activity could be obtained. Starting with 1.53 g of material having $[\alpha] = -216^{\circ}$, we obtained, after four recrystallizations from acetone at -78° , 0.56 g of 1,1'-binaphthyl having a specific rotation of $[\alpha] = -245^{\circ} \pm 1^{\circ}$ (Table XVI). We proceeded no further because the rotation did not increase in the last recrystallization.

Table XVI

Low Temperature Recrystallization of R- and S-1,1'-Binaphthyl

Recrystallization Number	Weight after Recrystallization, g	$[\alpha]$ after Recrystallization, degrees	$[\alpha]$ of Solution, degrees
R-(-)-1,1'-Binaphthyl:			
0	1.53 ^a	-216 ^a	
1	1.26	-228	-110
2	0.94	-244	-151
3	0.74	-247	-219
4	0.56	-245	-230
S-(+)-1,1'-Binaphthyl:			
0	1.41 ^a	+226 ^a	
1	1.19	+234	+202
2	0.95	+236	+220
3	0.70	+238	+225

^a Weight and specific rotation of initial material.

The activity of the material in solution was also monitored. When the solid is completely resolved, the material in solution should have the same activity as the recrystallized solid. However, our method of isolating the solute (by removal of solvent in vacuo at 25°) caused some

racemization, and the highest solute activity was therefore $[\alpha] = -230^\circ$. Assuming that after the fourth recrystallization the solution possessed $[\alpha] = -245^\circ$ at -78° , we estimated the loss in activity in recovering the solute from solution (based on a half-life of racemization of 11.4 h in benzene at 25° ⁷⁴) as 14° . It would not be possible, therefore, to observe a solute activity above 231° , close to the final observed value.

A sample of S-1,1'-binaphthyl was also recrystallized to see if the same specific rotation of the crystals ($[\alpha] = |245|^\circ$) could be obtained. The initial activity of the 1.41 g sample of S-1,1'-binaphthyl was $[\alpha] = +226^\circ$. After three recrystallizations, an activity of $[\alpha] = +238 \pm 1^\circ$ (0.70 g) resulted (Table XVI). The third recrystallization did not represent much of an increase over the second. The specific rotation of the recovered solute was 13° lower than that of the crystals, close to the estimated losses by racemization during solvent evaporation. Further recrystallizations were therefore not performed.

The increment in specific rotation on recrystallization of the solid can be seen from the ternary phase diagrams which describe the recrystallizing system at -78° (Figure 32). The phase relationships between solvent and R- and S-enantiomers when the latter form a racemate (Figure 32 (b)) have already been explained in Section 3.4.3 (p 95) and Figure 17 (p 102). This diagram represents the most stable ternary system at -78° . The phase system formed between the eutectic form and the solvent is also shown (Figure 32 (a)). Because of the imperceptible slowness of the solution phase transformation eutectic \rightarrow solution \rightarrow racemate at -78° (Section 3.4.1, p 83), the eutectic form can exist for indeterminable lengths of time at this temperature in contact with solvent.

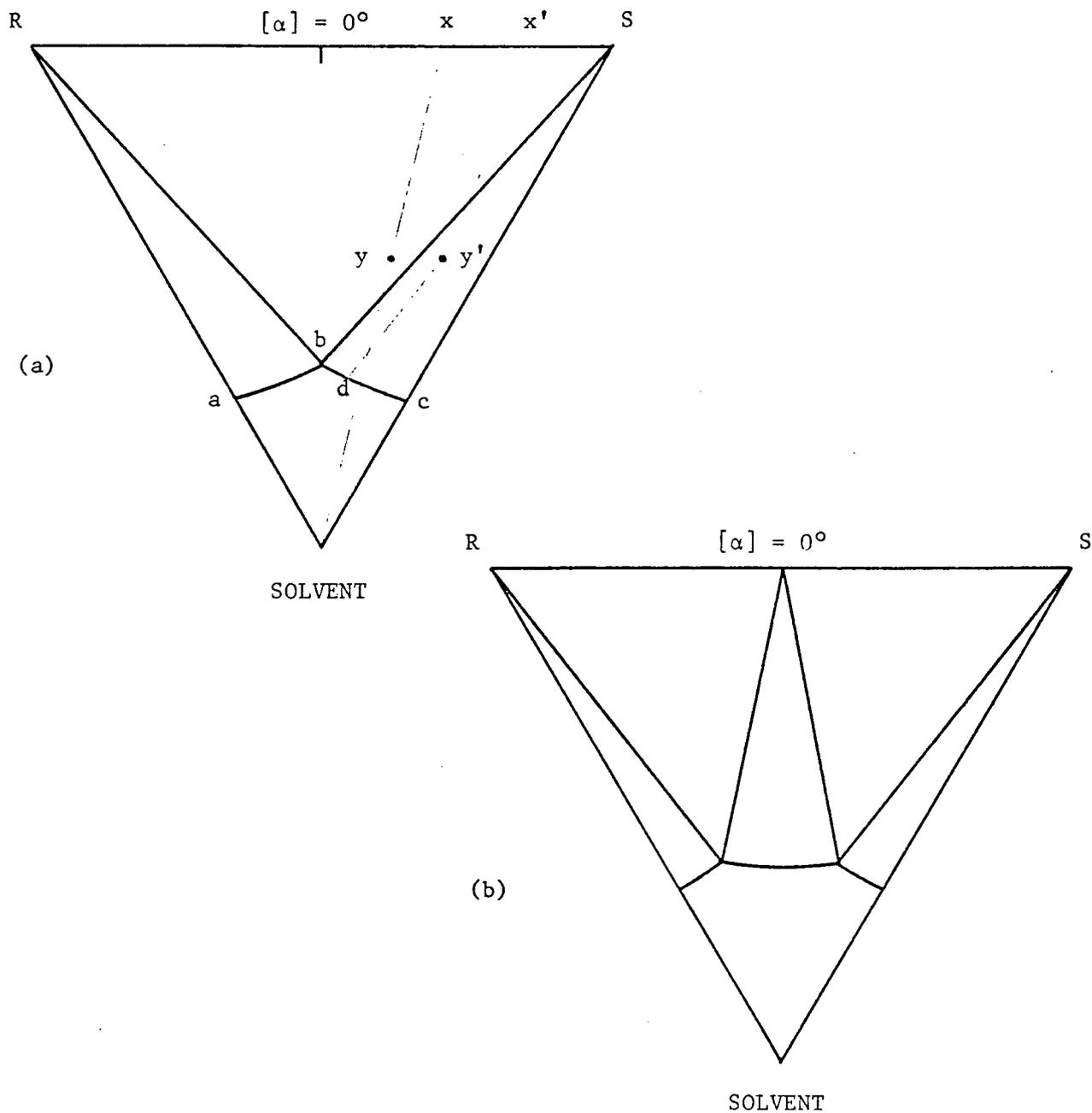


Figure 32. Schematic representation of the two possible ternary systems formed between solvent, R- and S-1,1'-binaphthyl at -78° . (a) R- and S-enantiomers form a eutectic mixture. (b) R- and S-enantiomers form a racemate. Although (b) is more stable, (a) can exist for indefinite periods of time at -78° .

Although the original samples in both of the above recrystallization sequences were the eutectic form (having been produced at 150°), the first batch of crystals could have been either form, or even both. That is, the "racemic part" of the less-than-fully-resolved samples could have been either a racemate or a eutectic mixture of R and S crystals, or both, after the first recrystallization.

Consider point y on the eutectic isotherm (Figure 32 (a)),^s which represents a possible allover composition of the solvent, R- and S-1,1'-binaphthyl mixture. At room temperature, the solubility curve abc will be found closer to the 1,1'-binaphthyl edge of the diagram, and y will be in the (single phase) solution region. At -78° , y will be in the (three-phase) R + S + solution region, so that precipitation can occur. If equilibrium in this eutectic ternary system is attained, then the solution will have composition b (racemic). The solid, however, will have a higher activity x' than it originally had (x). When x' is filtered from the solution and redissolved in acetone, the allover composition will now be y' (which, in this example, is in the two-phase R + solution region) at -78° . On attainment of equilibrium, the solid will be fully resolved R and the solution composition will be d, as determined by the tie-line Rd. Therefore, by such an equilibrium process, the excess of one enantiomer can be separated from a non-racemic material.^t

If attainment of equilibrium at -78° is particularly slow, a solid material having a rotation greater than x' may separate, leaving a metastable solution having an excess of the other enantiomer (R). When crystals

^s Similar considerations hold for the racemate isotherm (Figure 32 (b)).

^t By a similar process, the very small excess of one enantiomer in a "racemic" preparation can be made observable, as discussed on p 88.

and solution are separated, net resolution has been performed. Such nonequilibrium methods of resolution, usually accomplished by seeding racemic solutions, have been tried with a number of pairs of enantiomers.⁸⁵

In our crystallizations, the nonequilibrium process is probably operating to some extent, since duplicate crystallizations do not give material with the same rotation.

The limit of resolution which we have determined (+238°, -245°) should perhaps be referred to as a "phase limit" of resolution, since the terminal solid solutions^{50,51} existing at the edges of the binary R- and S-1,1'-binaphthyl phase diagram (Figure 14 (a), p 80) may have a composition range of a few percent. The R and S crystals obtained may thus be slightly optically impure. In this thesis, the value $[\alpha] = \pm 245^\circ$ is however taken as the fully resolved specific rotation, and where it is used, "percent resolution" has been calculated from this figure.

APPENDIX B

CALCULATION OF $\Delta G^{L \rightarrow H}$ AS A FUNCTION OF TEMPERATURE

In Section 3.3.2.3 (p 73), the statement was made that the enantiotropic ordering of racemic 1,1'-binaphthyl modifications (Figure 11 (b), p 67) could be proven by calculating the free energy difference between the racemate (low-melting) form and the racemic eutectic (high-melting) form, $\Delta G^{L \rightarrow H}$, as a function of temperature. However, a calculation of this difference at 150°C (423°K) using melting enthalpies and entropies of the two modifications gave a numerical result, $212 \pm 490 \text{ cal mole}^{-1}$, which was very imprecise when the limits of error were additively propagated through the calculation. Any solid-solid transition temperature τ resulting from an expression of $\Delta G^{L \rightarrow H}$ as a function of temperature would also be imprecise. However if our original goal of determining τ exactly is abandoned, some useful information can still be obtained from the calculation of the temperature dependence of $\Delta G^{L \rightarrow H}$, if only to see if it increases or decreases with temperature. Referring again to Figure 11, the monotropic system possesses an imaginary solid-solid transition point in the region where the melt is stable,^{51,81b} whereas in an enantiotropic system, the transition point is at lower temperatures. Therefore, some distinction between the two can be made by noting whether or not the free energy surfaces for racemate or eutectic converge or diverge in going to lower temperatures from 150°C.

The free energy difference at any temperature can be calculated if the enthalpy and entropy differences are known as a function of temperature. These, in turn, can be calculated from the heat capacity difference as a function of temperature, as follows.

Enthalpy and entropy are functions of state. Therefore, the enthalpy change in going from the racemate to the racemic eutectic (i.e., L→H) at any temperature T is equal to the enthalpy change in taking the racemate from T to 150°C (423°K), plus the change on going to the eutectic form at 150°C (which is known), plus the change on bringing the eutectic back to T. That is:

$$\Delta H_T^{L \rightarrow H} = \int_T^{423} C_p^L dT + \Delta H_{423}^{L \rightarrow H} + \int_{423}^T C_p^H dT$$

where C_p^L and C_p^H are heat capacities at constant pressure of the low- (racemate) and high-melting (eutectic) forms, respectively. This expression simplifies to:

$$[25] \quad \Delta H_T^{L \rightarrow H} = \int_T^{423} (C_p^L - C_p^H) dT + \Delta H_{423}^{L \rightarrow H}$$

Entropy can be treated in a similar fashion:

$$[26] \quad \Delta S_T^{L \rightarrow H} = \int_T^{423} (C_p^L - C_p^H) \frac{dT}{T} + \Delta S_{423}^{L \rightarrow H}$$

The free energy difference at temperature T is therefore:

$$[27] \quad \Delta G_T^{L \rightarrow H} = \Delta H_T^{L \rightarrow H} - T \Delta S_T^{L \rightarrow H}$$

We are interested in finding whether $\Delta G_T^{L \rightarrow H}$ increases or decreases with temperature from 150°C to, say, room temperature. As a first (and rather crude) approximation, we can assume that the enthalpy and entropy differences $\Delta H_T^{L \rightarrow H}$ and $\Delta S_T^{L \rightarrow H}$ are independent of temperature in the range of interest. Thus, $\Delta H_T^{L \rightarrow H} = \Delta H_{423}^{L \rightarrow H}$ and $\Delta S_T^{L \rightarrow H} = \Delta S_{423}^{L \rightarrow H}$, and it can be seen from Equations 25 and 26 that this approximation amounts to assuming that the heat capacities of both modifications are identical in this temperature range, i.e., $C_p^L = C_p^H$. The approximation greatly simplifies Equation 27, and substitution of our enthalpy and entropy values at 150°C gives $\Delta G_T^{L \rightarrow H}$ as a function of temperature:

$$[28] \quad \begin{aligned} \Delta G_T^{L \rightarrow H} &= \Delta H_{423}^{L \rightarrow H} - T \Delta S_{423}^{L \rightarrow H} \\ &= (1620 - 4.33T) \text{ cal mole}^{-1} \end{aligned}$$

The equation becomes that of a straight line, having a negative $\Delta G_T^{L \rightarrow H}$ value at 150°C, a zero value at 102°C, and becoming more positive at lower temperatures (Figure 33). Taking the uncertainties in $\Delta H_{423}^{L \rightarrow H}$ and $\Delta S_{423}^{L \rightarrow H}$ individually (dotted lines, Figure 33), the uncertainty in τ is $102^\circ \pm 52^\circ\text{C}$. This approximation therefore indicates that the system is enantiotropic with the racemate stable below about 102°C. However, we have observed the L→H transition as low as 76°C (Section 3.5.1, p 103). Taking these two observations together, we should more correctly conclude that the eutectic is stable at least from 150°C to 76°C, with the racemate becoming stable at lower temperatures.

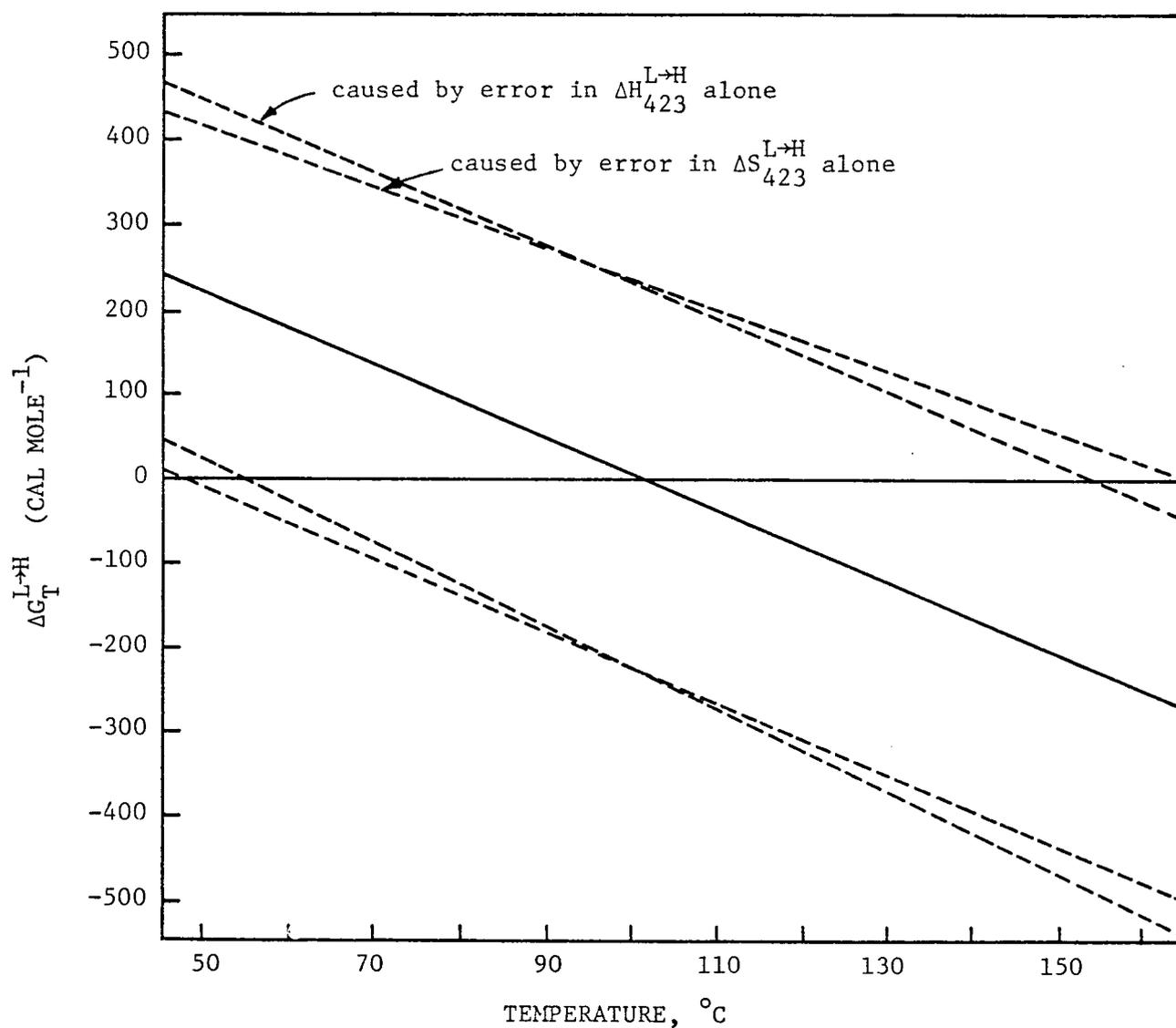


Figure 33. Relation of the free energy difference between racemate and racemic eutectic form of 1,1'-binaphthyl to temperature. First approximation, assuming $C_p^L - C_p^H = 0$ (see text). Dotted lines are uncertainties in $\Delta G_T^{L \rightarrow H}$ caused by errors in $\Delta H_{423}^{L \rightarrow H}$ and $\Delta S_{423}^{L \rightarrow H}$, taken individually.

As a second approximation, the quantity $C_p^L - C_p^H$ can be assumed constant from room temperature to 150°C. Equations 25 and 26 can be integrated to give:

$$[29] \quad \Delta H_T^{L \rightarrow H} = (C_p^L - C_p^H) (423 - T) + 1620 \text{ cal mole}^{-1}$$

$$[30] \quad \Delta S_T^{L \rightarrow H} = 2.303 (C_p^L - C_p^H) \log \left(\frac{423}{T} \right) + 4.33 \text{ cal deg}^{-1} \text{ mole}^{-1}$$

The quantity $(C_p^L - C_p^H)$ was determined on the d.s.c. The procedure⁴⁷ involved using a sapphire standard (for which C_p is known accurately as a function of temperature) and measuring C_p for both the racemate and the eutectic ($[\alpha] = -8^\circ$, i.e., almost racemic) form. The results are listed in Table XVII. Although the $C_p^L - C_p^H$ values at each temperature involve subtraction of two measured quantities, the rather large individual uncertainties are reduced by a factor of $\sqrt{10}$ by taking the mean of ten values. The difference $C_p^L - C_p^H$ is therefore $-13 \pm 4 \text{ cal deg}^{-1} \text{ mole}^{-1}$.

When the resulting free energy difference (Equation 27) is plotted against temperature, the solid line in Figure 34 results. The error in $\Delta G_T^{L \rightarrow H}$ introduced by the individual uncertainties in $\Delta H_{423}^{L \rightarrow H}$, $\Delta S_{423}^{L \rightarrow H}$, and $C_p^L - C_p^H$ is also shown (dotted lines). The uncertainty in $C_p^L - C_p^H$ does not cause nearly so large an error in $\Delta G_T^{L \rightarrow H}$ as do those in $\Delta H_{423}^{L \rightarrow H}$ and $\Delta S_{423}^{L \rightarrow H}$. As in the first approximation, the most probable value of the free energy difference becomes less negative as the temperature is lowered from 150°C, becoming zero at about 86°C. This most probable transition temperature τ is close to the lowest observed transition L→H (76°C). The second

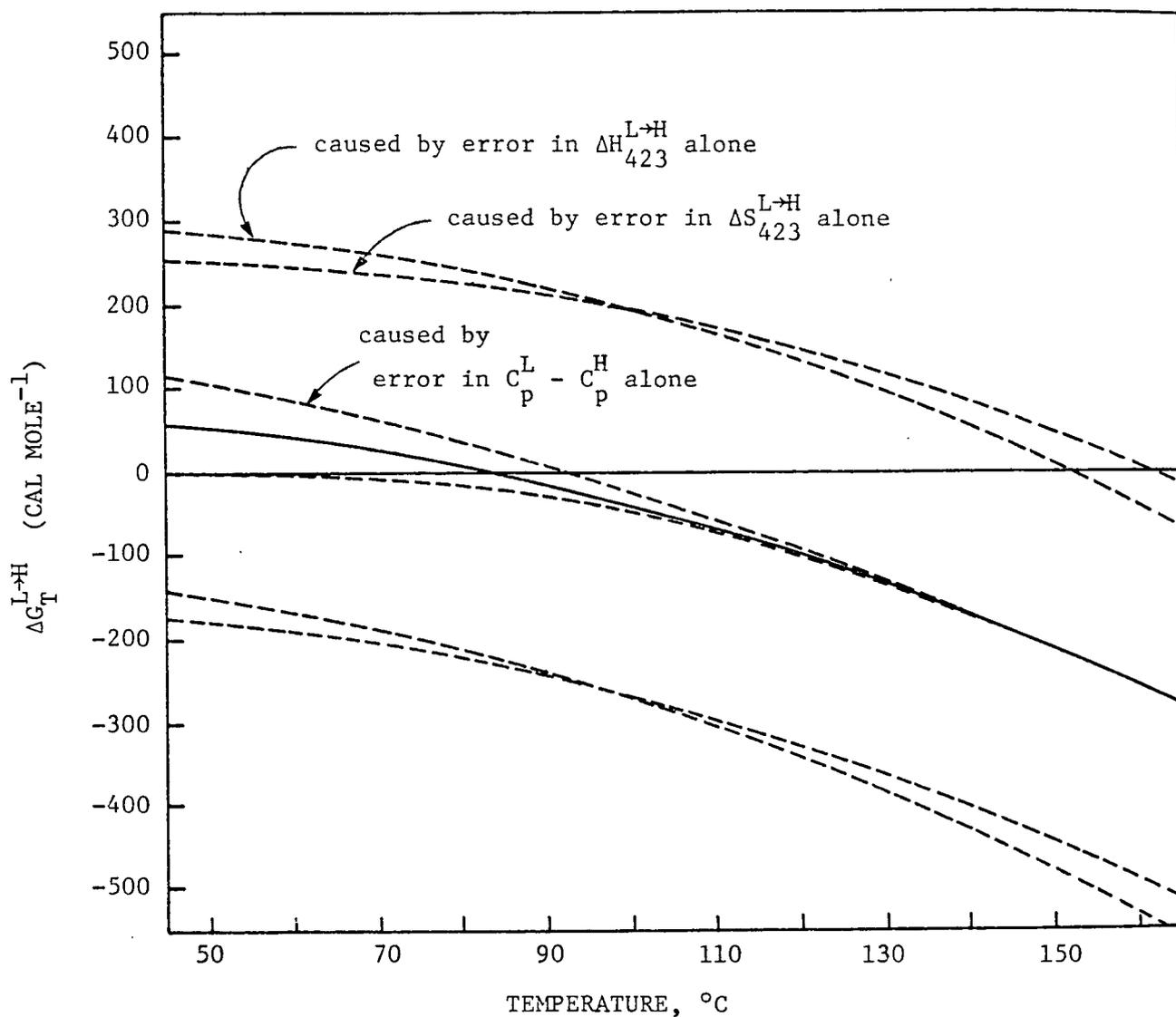


Figure 34. Relation of the free energy difference between racemate and racemic eutectic form of 1,1'-binaphthyl to temperature. Second approximation, assuming $C_p^L - C_p^H = \text{constant}$ (see text). Dotted lines are uncertainties in $\Delta G_T^{L \rightarrow H}$ caused by errors in $\Delta H_{423}^{L \rightarrow H}$, $\Delta S_{423}^{L \rightarrow H}$ and $C_p^L - C_p^H$, taken individually.

Table XVII

Heat Capacities at Constant Pressure for Low-Melting (Racemate) and High-Melting (Eutectic) Forms of 1,1'-Binaphthyl

Temperature		C_p^H ,	C_p^L ,	$C_p^H - C_p^L$,
C	K	cal deg ⁻¹ mole ⁻¹	cal deg ⁻¹ mole ⁻¹	cal deg ⁻¹ mole ⁻¹
50	323.16	85.7	71.7	14.0
60	333.16	87.6	73.8	13.8
70	343.16	90.4	76.3	14.1
80	353.16	94.3	82.1	12.2
90	363.16	96.2	85.4	10.8
100	373.16	98.2	85.5	12.7
110	383.16	99.7	87.1	12.6
120	393.16	101.6	90.1	11.5
130	403.16	105.8	92.8	13.0
140	413.16	112.9	96.9	16.0
150	423.16	117.9		<u>Mean</u> : 13.07

approximation therefore also implies that the racemic 1,1'-binaphthyl system is enantiotropic, with the transition temperature probably only slightly below 76 C.

A third approximation involves the determination of $C_p^L - C_p^H$ as a function of temperature. The individual heat capacity differences in Table XVII were fitted to a polynomial of the type $C_p^L - C_p^H = a + bT + cT^{-2}$ to obtain:

$$\begin{array}{rcl}
 a & = & -180.5 \qquad \pm 58.6 \\
 b & = & + 0.3511 \qquad \pm 0.1066 \\
 c & = & + 8.528 \times 10^{+6} \qquad \pm 2.589 \times 10^{+6}
 \end{array}$$

This polynomial^{108b} was substituted in Equations 25 and 26, and the three Equations 25, 26 and 27 were solved simultaneously for $\Delta H_{\tau}^{L \rightarrow H}$, $\Delta S_{\tau}^{L \rightarrow H}$ and τ . The transition temperature τ was 84°C, not much different from the value obtained from the second approximation. $\Delta H_{\tau}^{L \rightarrow H}$ and $\Delta S_{\tau}^{L \rightarrow H}$ were 772 cal mole⁻¹ and 2.16 cal deg⁻¹ mole⁻¹, respectively.

These thermodynamic calculations, performed with the measurements made with the differential scanning calorimeter, yield an imprecise value of τ but support an enantiotropic ordering of racemic 1,1'-binaphthyl modifications. A more exact value of the transition temperature could be obtained with the very precise methods of adiabatic calorimetry.^{59b}