

ENANTIOMERIC RECOGNITION AND INTERACTIONS

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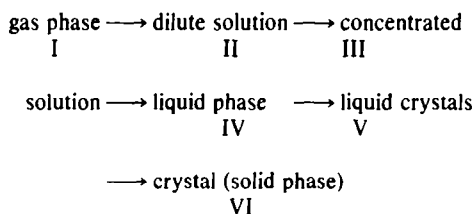
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(Received in UK 7 July 1976; Accepted for publication 10 August 1976)

Abstract—The consequences in a chemical reaction of the non-bonding interactions between molecules of one configuration on the one hand, and molecules of opposite configuration on the other hand are discussed. The reaction rates and product ratios in the reaction of a chiral compound depend upon the enantiomeric excess of the substrate. An antipodal interaction effect is observed in a phenol coupling reaction, a reductive camphor dimerization and a camphor reduction.

It is a matter of record that measurable differences in physical properties can be observed in solutions containing one enantiomer or its racemate. In 1895 Ladenburg¹ showed that the mixing of *R*- and *S*-coniine was accompanied by a change in temperature, while more recently Uskokovic² was able to show non-equivalence of the NMR spectra of racemic and optically active dihydroquinine due to diastereomeric solute—solute interactions of enantiomers in achiral solvents.^{3,20} In an excellent review of the available evidence Horeau³ concludes: "Certain effects observed by polarimeter, NMR and calorimetry can only be explained when the existence of diastereomeric interactions of enantiomers in solution are taken into account". He concludes by stating that the energy differences involved between the interactions of molecules of like configurations and molecules of opposite configurations "are too small to be used to change the optical composition of a mixture upon distillation". At no time is there any mention¹ of the possible consequences of these physical effects on the *chemical reactivity* of chiral substances.²¹

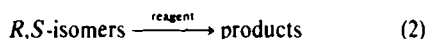
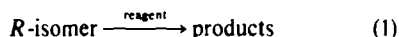
Both on the basis of symmetry consideration as well as on the basis of a free energy argument it is evident that the molecular surrounding of a *R*-isomer in solution is different from the molecular surrounding of that *R*-isomer in a *R,S*-mixture. In fact a sequence may be written as follows:



In phases I and II we may expect that no differences in physical properties are observable between one antipode and the racemate; ideal behavior is observed. As the solution becomes more concentrated the properties will differ from ideality and it is not surprising that Young *et al.*⁶ have observed local optical activity in a *racemic* liquid crystal.¹⁷ This can only mean that large (on a molecular scale) areas existed in the liquid crystal in which molecules of one configuration—on the average—associated more often with like molecules than with antipodes.

Notwithstanding the facts cited above, and the apparently large body of evidence gathered since 1850⁷ on the differences in properties between one antipode and the

racemate, no attention seems to have been paid to the consequences of these differences on the *chemical reactivity*. In symmetry terms we can see that eqn (1)



is neither identical nor enantiomeric with eqn (2) and consequently diastereomeric or different.

In eqn (1), any reaction performed on pure *R*-isomer will proceed, while this molecule is surrounded by—and thus has non-bonding interactions with—other *R*-molecules. In contrast in eqn (2), *any* reaction performed on a *R,S* mixture will proceed while the *R*-isomer is surrounded by—and thus in non-bonded interaction with—*R*- and *S*-molecules.

Thus it is evident that both the ground state energy as well as the transition state energy of a reaction performed on a solution containing merely *R*-molecules must differ from the ground- and transition-state energies of that same reaction performed on a solution containing the racemic mixture.

This difference in free energy of activation is the difference between $\Delta G^\ddagger_{R,R}$ (the ΔG^\ddagger for the forward reaction of the pure *R*-isomer) and $\Delta G^\ddagger_{R(S)}$, the ΔG^\ddagger for the forward reaction of *R*- in the presence of *S*-isomer. Although the difference, $\Delta G^\ddagger_{R,R} - \Delta G^\ddagger_{R(S)}$ may be small we may assume that this range might be 20–5000 cal/mol. This free energy difference may well be sufficient to cause noticeable differences in the reaction rates in the two systems, in the position of the equilibrium if we are dealing with a reversible reaction (epimerization) and finally in the product ratios.

Since we are dealing, when comparing reaction (1) and reaction (2), with two reactions which are identical in all respects except for the non-bonding interactions, small difference in $\Delta\Delta G^\ddagger$ may well affect the product ratios appreciably. Based on the considerations stated above we may state the following general principle: "When a chiral substance undergoes a reaction, the reaction rate and the product ratio will depend—inter alia—upon the enantiomeric excess present in the starting material".

It is necessary to stress that this entirely general statement differs in two respects with statements in the literature. In the first place, as pointed out earlier, all previous discussions concerning antipodal interactions have emphasized physical properties, including optical purity determination.³

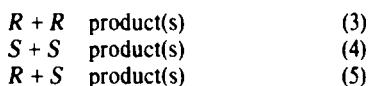
In the second place, in those discussions in which chemical transformations of one enantiomer are com-

pared to the reaction with a racemate ideal behavior has been assumed.*

The general statement above—an antipodal interaction effect—pertains to all reactions of chiral substances.

The reactions *between* enantiomers is worth considering as a special case. Many, well known reactions fall under this heading namely dimerization reactions (to form phenolic dimers, pinacols, olefins, or aldol products) and polymerization reactions.

When a racemate reacts with itself three reactions occur:



Reactions (3) and (4) are enantiomeric, (3) (or 4) and (5) are diastereomeric. We must distinguish two separate effects. First the “*enantiomeric recognition*” effect. This is a fairly well established concept and has reasonably adequate experimental and theoretical support.^{9,10,18}

If ideal behavior were observed reaction (3) (or 4) and (5) could still show different kinetics and products. If we consider a non-bonding interaction (which may show a good or bad “fit”) as the beginning of the reaction coordinate then the formation of the bond can be considered as the terminus of the process. Simply stated, an *R*-isomer sees its *S*-isomer differently from another *R*-isomer.

In addition to the effect discussed above, a second effect is present, namely an “*antipodal interaction*” effect. It is concerned with the effects of a chiral surrounding upon the reaction itself. Our entire argument is based on realization of non-ideal behavior.

Consider again the reaction between *R* and *R*. If this reaction takes place in “optically pure” *R*, some interactions of the reacting molecules during the entire reaction sequence, are with other *R* isomers. If on the other hand the reaction between *R* and *R* → products takes place in a medium containing *S* as well (for example the racemic case) than some of the interactions of the reacting molecules will be with *R* and some with *S* isomers.

The differences in these interactions (the antipodal interaction effect) will manifest itself in the products or product ratio of reaction (3) (or 4).

The importance of this general statement rests not only upon the realization that the chiral surroundings are different in a system containing one enantiomer from a system containing its racemate but also upon the implication that this difference in chiral surroundings can influence reaction rates and products ratios.¹¹

The antipodal interaction effect becomes of importance in studying asymmetric transformations and will be subject to a number of influences:

(a) Non-bonding interactions between reactants must be present. In this connection it is perhaps worthwhile to point out that a multitude of non-bonded interactions exist outside the carefully documented areas of hydrogen bonding.¹² The antipodal interaction effect (on chemical reactions) will therefore be highly concentration and solvent dependent and may well be studied optimally with chiral liquids, liquid crystals or highly concentrated solutions.¹¹

(b) Possible complex formation between reactants and reagents. It is evident that when a reaction proceeds in such a manner that intermediate complexes of the type (reactant)_n-metal are formed, diastereomeric complexes

will be present in a solution containing the racemate and absent in a solution containing one enantiomer. The influence of such a complex on the rate of the reaction and the product ratios will depend upon the rate determining step.

The considerations as outlined above lead one to the conclusion that a detailed study of “antipodal interaction” effect, although this effect may be viewed as a second order effect, may also become an important tool in elucidating the fine details of the molecularity and kinetics of a reaction. No cases are known to us in which a reaction with a racemate and the same reaction with one enantiomer have been examined in sufficient detail to warrant conclusions regarding the antipodal interaction effect.

We have attempted to examine some reactions for the “antipodal interaction” effect, namely the oxidative dimerization of a chiral phenol (system A) and the reductive dimerization of camphor (system B). The third system investigated was the *R*- and *R,S*-camphor reduction (system C).

System A

The oxidative dimerization of optically pure *S*(+) - 7 - hydroxy - 1,5,6 - trimethyl - 1,2,3,4 tetrahydronaphthalene (1) and of racemic 1 proceeded according to Scheme 1.¹⁴ The total yield of the dimer fraction in both cases was 62%.

The coupling of racemic monomer 1 shows that there is a preference for coupling of two monomers with the same configuration (Enantiomeric recognition effect).

Dimerization of *R,S*-monomer yielded in 73.9% (*SS, RR*)-dimer, due to coupling of two monomers with the same configuration and 26.1% *RS* dimer, due to coupling of two monomers with enantiomeric configuration.

In addition a difference between the reaction of racemic (*R,S*) monomer and the reaction of optically pure monomer is observed, in the fact that reaction of *S*-monomer with *S*-monomer proceeded via a stereospecific way in giving only *SS trans*-dimer in the case of the optically pure substrate.

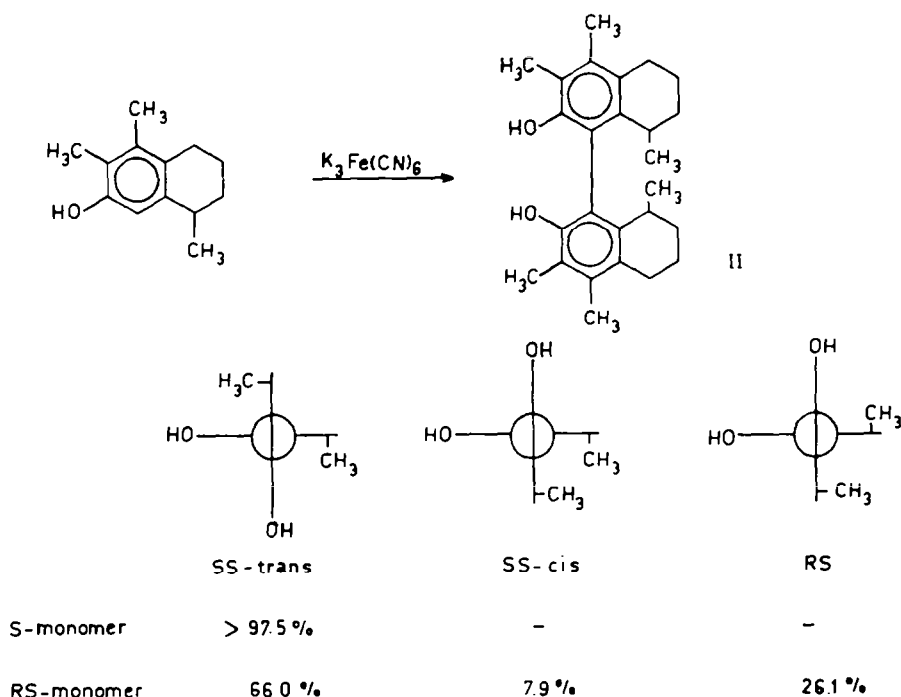
In the racemic case also 7.9% of the (*RR,SS*)-*cis* dimer is observed. This striking difference between the 7.9% isolated and identified *SS cis*-dimer in the latter case and its absence in the first case means that there must be an influence of the *R*-antipode of the reaction of the *S*-monomer, in the racemic case, which influence is not present when only *S*-monomer is the substrate (“antipodal interaction” effect).

System B

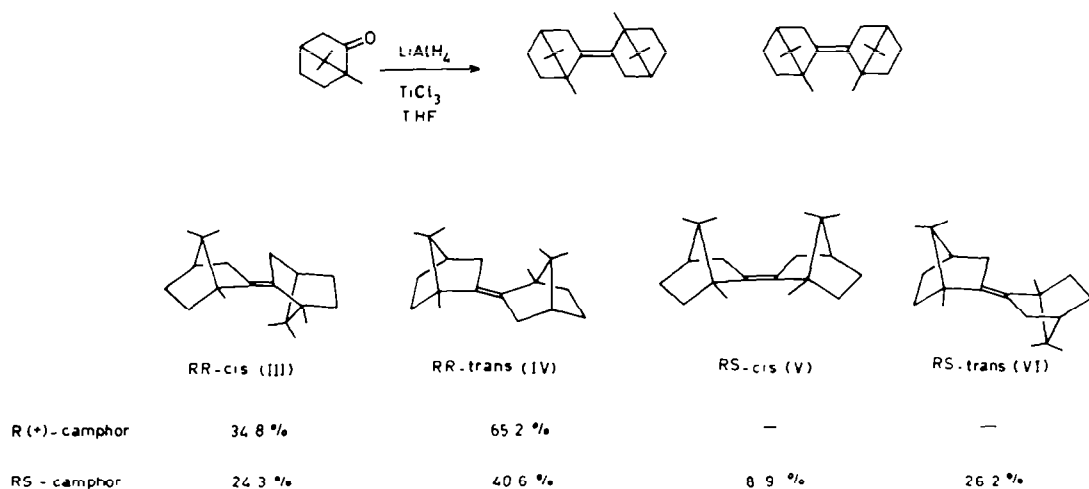
The reductive dimerization of *R*- and *RS*-camphor according to McMurry's method¹⁵ gave a mixture of *RR-cis* and *RR-trans* bornanylidenebornanes (3 and 4) in the first case and a mixture of (*RR,SS*)-*cis* (3), (*RR,SS*)-*trans* (4), *RS-cis* (5) and *RS-trans* (6) in the second case (Scheme 2).

In the formation of these bornanylidene-bornanes a preference for the dimerization of two monomers with the same configuration is also observed (“enantiomeric recognition”).

The (*RR,SS*)-*cis* and (*RR,SS*)-*trans* isomers are formed in 64.9% yield. The formation of these isomers (3 and 4) is due to coupling of two monomers with the same



Scheme 1. Coupling of phenol I.



Scheme 2. Reductive dimerization of camphor.

configuration. The coupling of monomers with antipodal configurations gave the *RS-trans* (6) and *RS-cis* (5) dimers in a total amount of 35.1%.

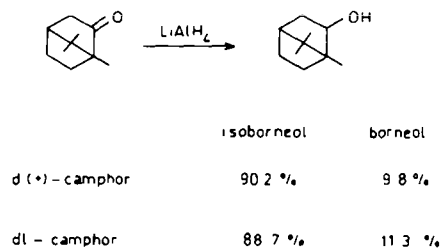
For the "antipodal interaction" effect a comparison between the reactions of optically pure camphor and of racemic camphor must be made. In the first case, the reaction between *R*-monomer and *R*-monomer yielded *RR-cis* (3) and *RR-trans* (4) in a ratio 34.8:65.2. In the racemic case, where an influence of the enantiomeric monomer on the reaction of *R*-monomer is possible, gave the reaction of *R*-monomer with *R*-monomer these isomers (*RR,SS*-*cis* (3) and (*RR,SS*)-*trans* (4) in a ratio 37.4:62.6.

In this dimerization reaction an "antipodal interaction" effect is again observed. This effect must be due to *R*-camphor-*S*-camphor interactions when *R*-monomer reacts with *R*-monomer.

System C

The only general system we have studied so far was the reduction of *R*- and of *R,S*-camphor to borneol and iso-borneol (Scheme 3).¹⁶

The results based on a large number of reductions run under identical conditions, indicate that reproducible

Scheme 3. Reduction of *R* and *R,S*-camphor.

difference is present in the product ratio of the two reductions. The influence of the *S*-molecules during the reduction of *R*-camphor in the case of racemic substrate is only small, resulting in a small "antipodal interaction" effect. This is in agreement with the expected weak non-bonded interactions between camphor-molecules in solution.

As in these reductions 1 equivalent LiAlH_4 was used per mol of camphor it is very well possible that complexes of the type LiAl(OR)H_3 , $\text{LiAl(OR)}_2\text{H}_2$, $\text{LiAl(OR)}_3\text{H}$, etc. are present.

Several molecules of the substrate could be incorporated in the reagent. The formation of intermediate diastereomeric complexes is only possible in the racemic case. It is not clear which part of the "antipodal" effect is due to these "difference" in reducing agent in the reduction of racemic- and of optically pure camphor.

Comparing the three systems investigated, it is seen that although there is a striking difference between the reaction of optically pure—and racemic substrate in the phenol coupling reaction, only small differences were observed in the camphor dimerizations and the camphor reductions.

The differences between the three systems are probably due to the great difference in type of reaction and the great difference in substrate.

As the "antipodal interaction" effect is determined through non-bonded interactions and complex formation, a great dependance on substrate, concentration, solvent, reagent, etc. is expected. It is therefore clear that different substrates, reactions and reaction conditions are needed to optimize the "antipodal interaction" effect.

A reaction in the nematic phase of a liquid crystal would be worthy of study since regular non-bonded interactions cause the nematic phase to exist.

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