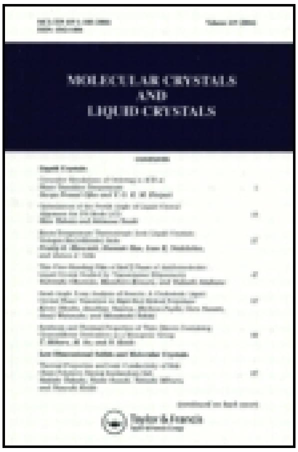


Molecular Crystals and Liquid Crystals Incorporating Nonlinear Optics
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gmcl17

Enantiomer-Associations Influencing Chemical Reactivity

M. Aacs [a], T. Gizur [b], I. Péter [b], K. Harsányi [b], Zs Jászay [a] & E. Fogassy [a]

[a] Department of Organic Chemical Technology, Technical University Budapest, POB 91, H-1521, HUNGARY

[b] G.Richter Pharmaceutical Works, Budapest, POB 17, H-1475, HUNGARY

To cite this article: M. Aacs , T. Gizur , I. Péter , K. Harsányi , Zs Jászay & E. Fogassy (1990): Enantiomer-Associations Influencing Chemical Reactivity, Molecular Crystals and Liquid Crystals Incorporating Nonlinear Optics, 187:1, 289-296

To link to this article: http://dx.doi.org/10.1080/00268949008036053

Mol. Cryst. Liq. Cryst., 1990, vol. 187, pp. 289–296
Reprints available directly from the publisher
Photocopying permitted by license only

Printed in the United States of America

ENANTIOMER-ASSOCIATIONS INFLUENCING CHEMICAL REACTIVITY.

M. ÁCS,* T.GIZUR,** I.PÉTER,** K.HARSÁNYI,** ZS. JÁSZAY* & E.FOGASSY*
*Department of Organic Chemical Technology, Technical University Budapest, POB 91. H-1521 HUNGARY
**G.Richter Pharmaceutical Works, Budapest, POB 17. H-1475 HUNGARY

Abstract A comparative study for a ring-closure reaction in solution, melt and solid state is reported. The different behaviour of the different enantio-composition is explained on the basis of enantiomer-associate formation.

INTRODUCTION

Enantiomers (ꟻ,F) have a tendency to form associations that can be enantiomers and diastereoisomers relative to each other (Figure 1). These associations, depending on the strength of the bonds formed and the lifetime of these interactions, can greatly influence the outcome of a chemical reaction, even under achiral conditions[1].

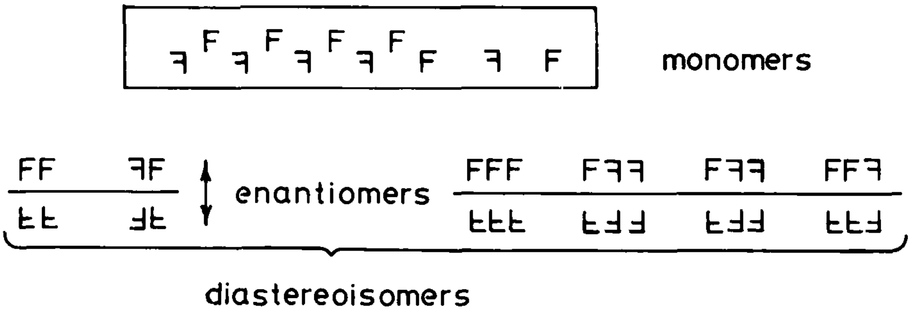


FIGURE 1. Association-forming possibilities for enantiomeric species. The diastereoisomeric relationship between homo- and heterochiral associations results in different chemical reactivity, even under achiral reaction conditions.

Since the dominant theories in preparative organic chemistry have treated the enantiomeric molecules in solution as separately solvated chemical entities, no demand has emerged for comparative studies of reactions which start from the racemic, non-racemic and optically pure substances. However, during the past 25 years papers have appeared reporting different analytical and chemical behaviour for solutions of enantiomeric and racemic species. These differences can be well understood on the basis of the classical three-point interaction model.[2] The same model gives an explanation why in most cases the existence of these associations can be neglected (Figure 2).

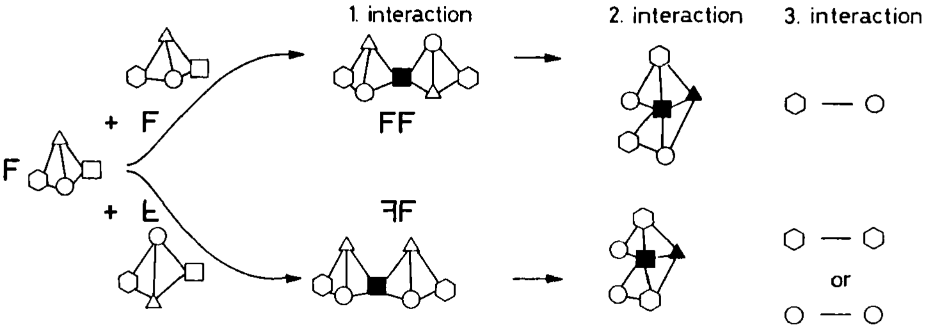
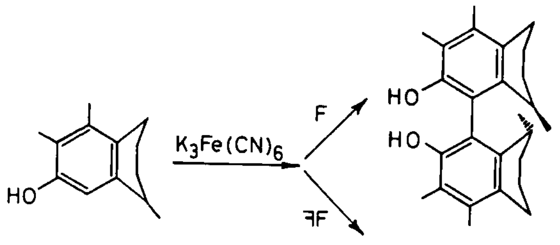


FIGURE 2. Differences resulting in different analytical and chemical properties for the dimeric associations, based on the three-point interaction model.

For clarity, the enantiomers (ꟻ,F) are represented by asymmetrically substituted tetrahedra. As Figure 2. clearly shows, establishment of the first "two" interactions is equally possible and probable for the homo and heterochiral dimers. However the third interaction possibility is different for the ꟻ,ꟻ and FF/ꟻꟻ dimers. If this "third" connection mannifests itself as a hydrogen bridge or charge-transfer interaction, then differences in nmr-[3] or UV-spectra[4] can be observed.

MANIFESTATION OF ENANTIOMER-ASSOCIATES.

The influence of such associations on the outcome of a reaction was first described by WYNBERG and FERINGA.[5] They observed different stereoisomeric ratios for the product depending on the enantiomer composition in the starting materials during the oxidative dimerization of a chiral tetrahydro-naphtalene derivative (Scheme 1) and in the reductive dimerization and hydrogenation of camphor. However clearcut evidence for the stable enantiomer associations in solution had not been reported. The use of an external chemical agent allows the "supposition" of a preformed complex between the oxidant and the reductant and one of the monomers.



SCHEME 1.

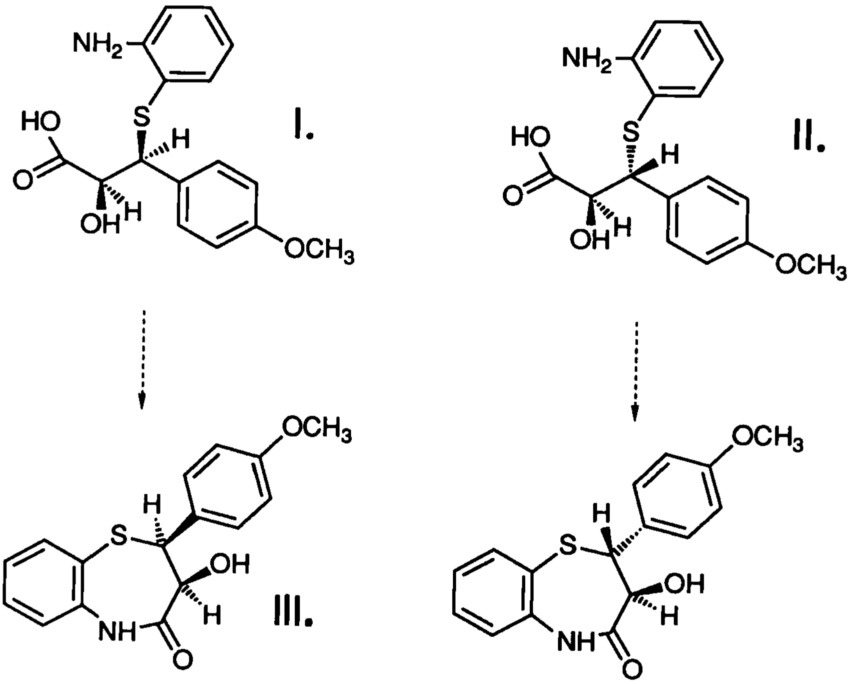
trans F-F

starting material	product
F	trans-F-F
	cis F-F/ꟻ-ꟻ
ꟻF	meso F-ꟻ
	trans F-F/ꟻ-ꟻ

This complex which is a chemically altered species can differentiate in a kinetically controlled reaction between the enantiomeric monomers. To avoid the problem of the preliminary "complex" formation between the substrate and the reagent, one has to accomplish monomolecular reactions in the absence of any auxiliary reagent.

"ANOMALOUS" BEHAVIOUR OF A MONOMOLECULAR RING-CLOSURE REACTION

As a model reaction for these studies an intramolecular ring-closure of I and II has been chosen (Scheme 2.).[6] Upon heating a ring-closure takes place at different



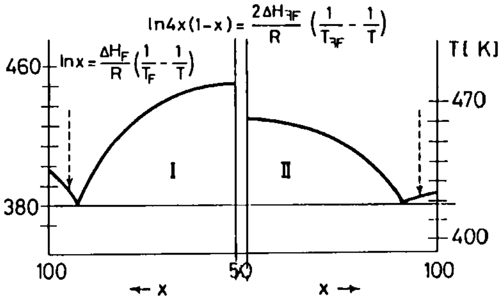
SCHEME 2.

reaction rates for the different enantio-compositions, (Table I.), with the optically pure compounds reacting faster than the racemates.

TABLE 1. Results for the ring-closure reaction carried out in xylene at reflux.

compound	starting enantio composition	reaction time (h)	resulted yield (%)	resulted enantio composition	remarks
I	100 : 0	3 - 4	84	100 : 0	all reactions were carried out until no starting material was detectable.
	50 : 50	6 - 7	84	50 : 50	
	90 : 10	3 - 4	68	100 : 0	
	95 : 5	3 - 4	80	100 : 0	
	94 : 6	3 - 4	79	99 : 1	
II	100 : 0	11	68	100 : 0	reaction time defined by the fastest reaction
	75 : 25	11	84	90 : 10	
	50 : 50	11	42	50 : 50	

Although both the starting material, and the product are nearly insoluble, there are solubility differences for the different enantio-compositions. Therefore the reaction rate differences may be linked with the differences in solubility. To establish this possibility, ternary (solubility) phase diagrams must be constructed. Relying on JACQUES and LECLERC's observation[7] instead of accomplishing this time-consuming and laborious experimental work, we constructed the binary phase diagram which clearly illustrates that both I and II are forming true racemates (racemic compounds), with higher melting points, and consequently lower solubility than the corresponding enantiomers (Figure 3).



sample	melting point T in K	heat of fusion ΔH in cal/g
(+)-I	409	20.6
(±)-I	451	45.1
(+)-II	452	68.3
(±)-II	462	71.2

Fig.3. Binary phase diagrams for compounds I and II, constructed by using the Schröder-van Laar and Prigogine-Defay-Mauser equations. Heat of fusion (ΔH) and melting points (T) were recorded by DSC.

These diagrams are in a good agreement with the experimental results for the compound II (the erythro diastereoisomer), where the shortest reaction time was characteristic of the most soluble (eutectic) composition. In contast, for the threo-series, with incomplete conversions, we obtained different optical purities, indicating that additional factors influence the reaction. Moreover, when recording the melting processes, a well-reproducible exothermic peak (ca. 20 degree lower than the melting point), appeared in the thermogram of the optically active sample. A sharp melting peak is characteristic of the racemate. The exothermic peak may be observed when melting any non-racemic mixtures (Figure 4).

These findings may be explained by a) partial decomposition, b) epimerization or racemization, c) ring-closure d) polymorphic (conformational) transformation. Fortunately versions a) and b) could be excluded and version c) established by the same run. A repeated melting procedure with an extended temperature limit

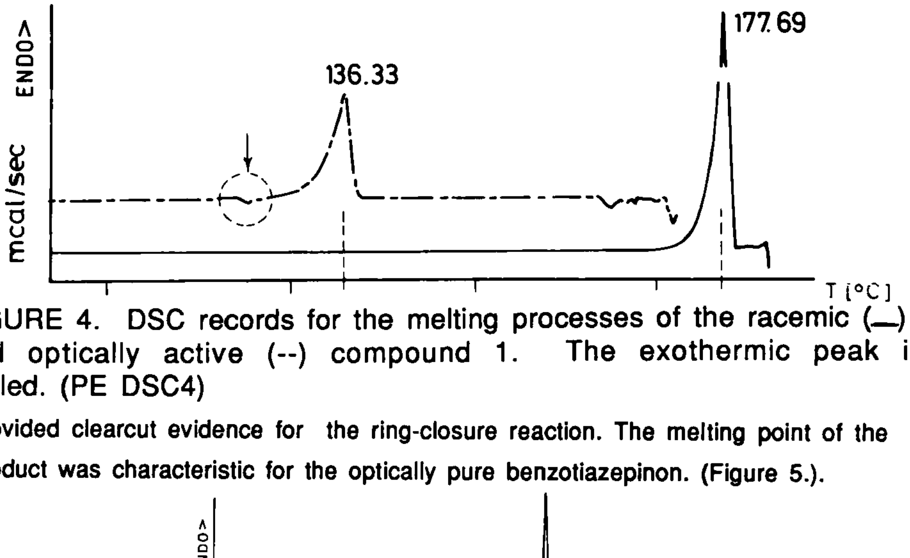


FIGURE 4. DSC records for the melting processes of the racemic (—) and optically active (--) compound 1. The exothermic peak is circled. (PE DSC4)

provided clearcut evidence for the ring-closure reaction. The melting point of the product was characteristic for the optically pure benzotiazepinon. (Figure 5.).

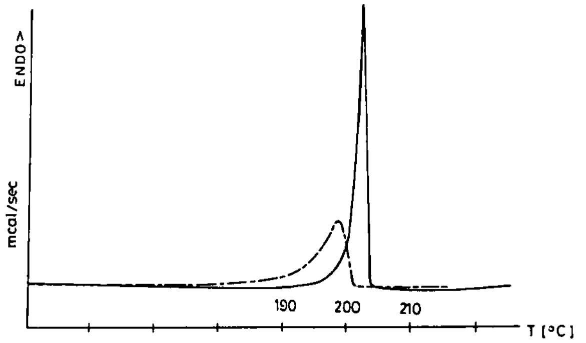


Fig.5.DSC records for the optically active bezotiazepinon (III) obtained by a regular ring-closure reaction, in solution (—) and for the (+)-I held at 120°C during 1^h (--). *(recorded by Perkin Elmer DSC 4)*

The larger scale experiments at different temperatures provided the ring-closured product at a higher conversion than those carried out in solution at reflux. The yields were lower for the racemate (Table 2.).

TABLE 2. Ring-closure at different temperature.

compound	temperature (oC)	reaction time (min)	yield (%)	remarks
(+) -I	135	180	84	in xylene
	135	5	95	in melt
	125	90	98	in solid state
(±)-I	135	540	84	in xylene
	176	5	70	in melt many by-products
	125	120	-	no reaction occurs

The polymorphic transformation can not be excluded. A conformational change in the crystalline state may be required for the right arrangement for a ring-closure reaction.

As we have not obtained the same reactions for the racemate and the optically active isomers, we sought the reasons for these striking differences.

A POSSIBLE RATIONALE FOR THE REACTIVITY DIFFERENCES

Although the reactivity differences in solution clearly indicate stronger hindrance for the racemate ring-closure than the non-racemic enantiomer mixtures of compound I, the almost total insolubility of the "neutral amino acids" provides no evidence for the existence of the relatively stable homo- and heterochiral associations, in solution. (The ^{1}H-nmr spectra of (+)-I and the (±)-I in DMSO are identical). Still the reactivity differences prompted the search for some detectable differences.

Interestingly (but not surprisingly) the IR-spectra exhibited very pronounced differences. (For the different packing and interaction possibilities in the solid state, the enantiomers and the true racemate always show up as slightly too strongly differing IR-spectra.). In these cases the differences are more marked.

The racemate contains fully ionized carboxylic acid and amino groups and only one type of hydrogen-bonded hydroxy group. In the optically active sample, signals characterizing unionized and ionized amino and carboxylic groups can be discovered, moreover three types of hydrogen-bridged hydroxy groups make the spectra more complicated (Figure 6.).

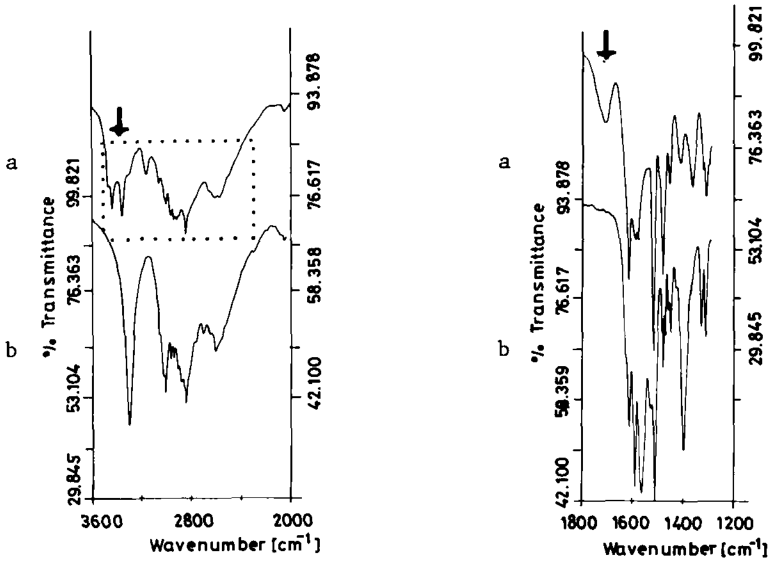


Figure 6. Parts of the IR-spectra characteristic for the differences of *a*) (±)-I and *b*) (+)-I . Bands of the free amino and carboxylic groups (↓) are missing from the spectrum *a;* a diffuse area of hydrogen-bonded hydroxy groups (...) makes the differences more pronounced in spectrum *b.* (*Nicollett 20-DXC ft-ir spectrometer*)

This effect may be derived from the different structural arrangement possibilities in the homo and heterochiral associations. Starting from the fact that the racemate is a molecular compound, the crystal structure can be constructed from the dimers of the zwitter-ionic form of the mirror image components (Figure 7*a*.), where the neighbouring (α) alcoholic hydroxy and the carbonyl group of the ionized carboxyl groups can form an internal hydogen-bond (as usual in α-hydroxy acids). Such an arrangement would be in a good agreement with the IR-spectrum. For the optically active compounds one should force one's imagination and come to a more complicated system, a tetramer which is held together again by the hydrogen-bonded amino and carboxyl groups that are, in this case, derived from different "parent" species. In this way the existence of the free amino and carboxyl groups and the different types of the hydrogen-bonded hydroxy groups can be rationalized.

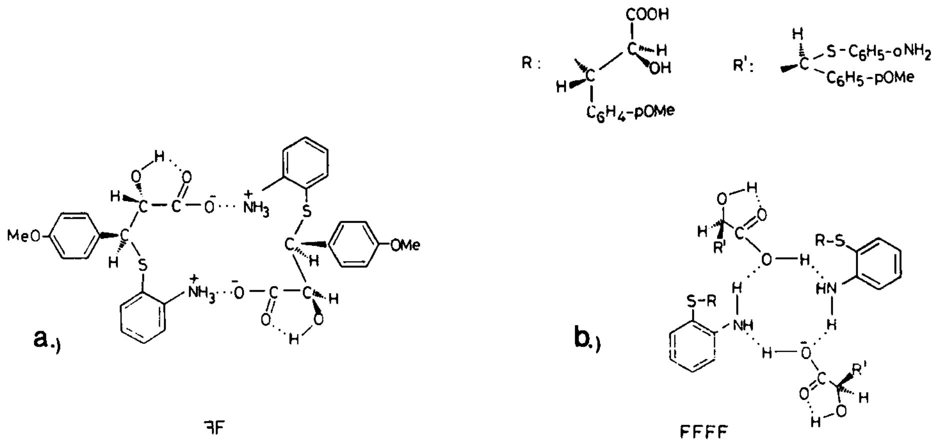


Figure 7. Possible arrangement of dimers and tetramers in the solid state structure of racemic (*a*) and optically active (*b*) compounds I.

CONCLUDING REMARKS

A comparative study of the same ring-closure reaction of the racemate and its enantiomer, in solution, in melt and in solid state has revealed,on a labororatry scale, that the importance of differences in reactivity between (diastereoisomeric "enantiomer") associations must be considered. A few examples have already been published where the enantiomer reacts considerably faster then the racemate, meaning that during the next chemical reaction-step, one can get enantiomerically richer product than the starting material. This association effect should be especially strong in the case of the natural and unnatural amino acids, hydroxy acids, hydroxy amines, where a great variety of hydrogen-bonded systems can be produced and where diastereoisomeric association differences may be more pronounced.

REFERENCES.

1. E. Fogassy, F. Faigl and M. Acs, Tetrahedron Lett., 22, 3093 (1981).
   Tetrahedron, 41, 2841 (1985).
2. A Ogston, Nature, 162, 963 (1948).
3. T. Williams, R. G. Pitscher, P. Bommer, J. Gutzwiller and M. Uskokovic, J. Am. Chem. Soc., 91, 1871 (1969).
   A. Horeau and J. P. Guette, Tetrahedron, 20, 1923 (1974).
4. W. H. Pirkle and T. C. Pochapsky, J. Am. Chem. Soc., 109, 5975 (1987)
5. H. Wynberg and B. Feringa, Tetrahedron, 32, 2831 (1976).
6. B. Kojic-Prodic, et al., Helv. Chim. Acta., 67, 916 (1984).
7. M. Leclercq and J. Jacques, Bull. Soc. Chim. Fr., 2052 (1975).