

# The Quest for Relationships between Conformation and Chiroptical Properties: From Solution to Solid State

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Dedicated to the late Prof. Ernest Ludwig Eliel *in memoriam*

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**Abstract.** The enormous interest of the late Prof. Ernest Ludwig Eliel for stereochemical problems has led not only to his publication of a impressively long list of papers, books and countless invitations for keynote lectures at conferences, but has stimulated a similar interest in this field among the many who have had the opportunity to work with him. Ernest's seed on one of us turn out in the quest for new relationships between conformation and chiroptical properties. The germ was a simple molecule, *cis*-3-hydroxythiane *S*-oxide, that enabled us to show that the specific rotation at any position of its conformational equilibrium is a weighted average of the specific rotation of the individual conformations. We are now currently involved in the challenging task of the controlled building of solid structures from bottom-up approaches. To this end we have covalently attached optically pure phosphonates within the layers of  $\gamma$ -zirconium phosphate leading to chirality at the supramolecular level. We have shown that conformation and chiroptical properties are also strongly intertwined in the solid state.

**Keywords:** Eliel, chiroptical properties, conformation, zirconium phosphate, laminar materials, supramolecular chirality.

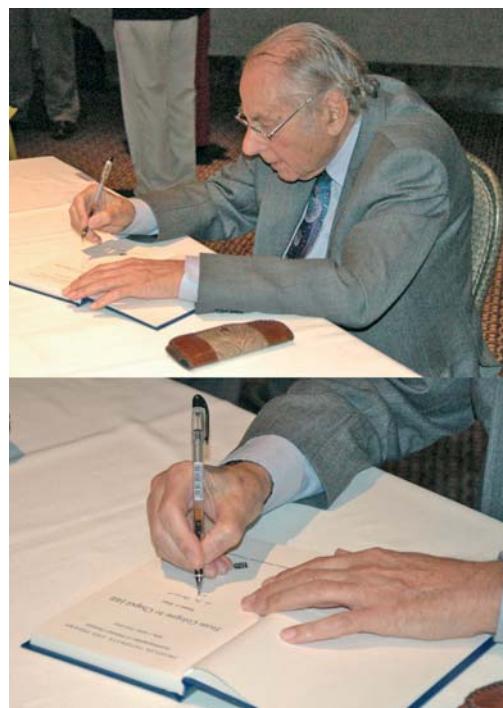
## Introduction

For all of us, organic chemists, the name of Eliel is immediately associated to Stereochemistry in capital letters. The late and beloved Professor Ernest Ludwig Eliel (Figure 1) continues exerting intense influence in a countless number of students, researchers and colleagues because his books on Stereochemistry of Organic Compounds still are at the cutting edge of the field (Figure 2) [1]. It has to be stressed that few are the manifestations of chemistry not directly or indirectly related to a dissymmetric space.

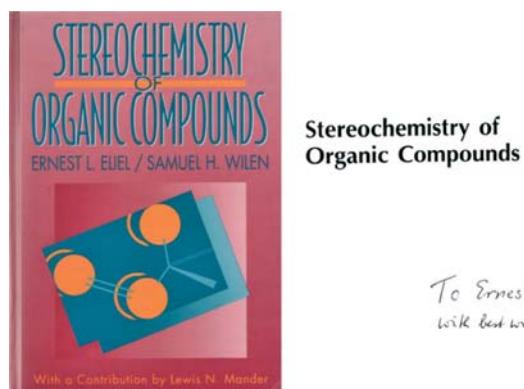
Ernest allowed us to savor some of his scientific and personal feelings through the reading of his outstanding autobiography (Figure 3) [2]. The editor of the book, Jeffrey I. Seeman, wrote a fine paper in Chirality's special issue dedicated to Eliel, outlining a concise, yet rigorous, juicy and expert appraisal of Eliel's most salient achievements [3]. However, only a few of us have had the privilege of personally enjoying his mastery in the tackling of all kinds of stereochemical problems and of chemistry in general. The intellectual seeds which he implanted in the minds of all of us who had the opportunity to stay in his laboratory (Figure 3), have ripened through time in many different ways. The current involvement of my research group in Supramolecular Chemistry and, most particularly, in the problem of Chirality under Confinement is an example.

**Resumen.** El enorme interés por los problemas estereoquímicos de toda índole mostrado por el tristemente desaparecido Prof. Ernest Ludwig Eliel ha dado lugar, no sólo a su larga y notoria lista de publicaciones, libros y conferencias, sino al no menos importante hecho de dejar la huella de su preocupación en muchos de los que tuvimos la enorme suerte de trabajar con él. En este trabajo describimos cómo Ernest sembró en uno de nosotros la necesidad de buscar relaciones entre propiedades conformatacionales y quirópticas. La semilla fue una molécula sencilla, el *S*-óxido del *cis*-3-hidroxitiano, en la que mostramos que la rotación específica en cualquier posición de su equilibrio conformatacional es una media ponderada de la rotación específica de las conformaciones individuales. En el presente estamos dedicados a la construcción de estructuras sólidas. La unión de fosfonatos ópticamente puros entre las capas del  $\gamma$ -fosfato de zirconio da lugar a quiralidad a nivel supramolecular. Hemos mostrado que los términos conformatión y propiedades quirópticas también están íntimamente relacionados en el estado sólido.

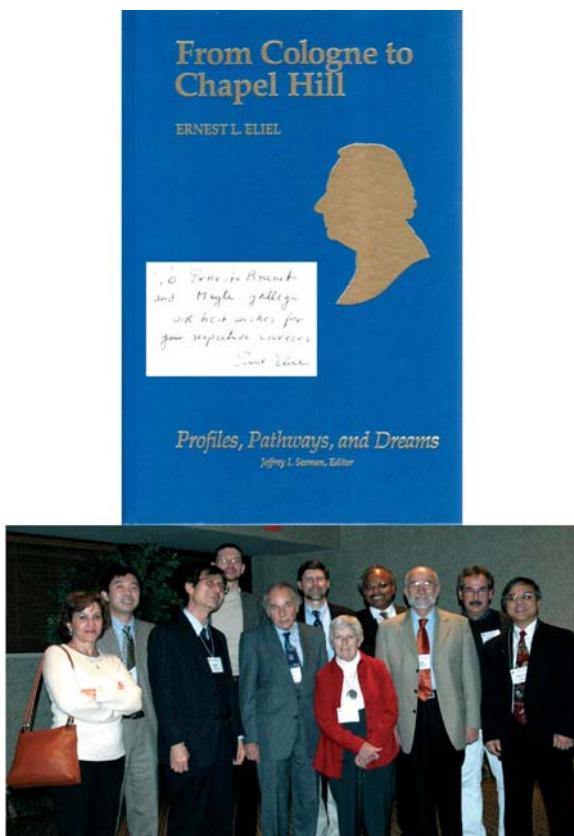
**Palabras clave:** Eliel, propiedades quirópticas, conformatión, fosfato de zirconio, materiales laminares, quiralidad supramolecular.



**Fig. 1.** Professor Ernest Ludwig Eliel signing his book "From Cologne to Chapel Hill" at the ACS 56th Southeast Regional Meeting 2004 (November 10-13, 2004).



**Fig. 2.** Eliel's ultimate version of his book "Stereochemistry of Organic Compounds" co-authored with his good friend (the late) Samuel H. Wilen; Eliel's handwritten dedication to this article's author.



**Fig. 3.** Hardcover of Eliel's autobiography and dedication (inset); Eliel and wife Eva (center) with some of the former graduate students and post docs, attendants to the ACS 56th Southeast Regional Meeting (November 10-13, 2004); from left to right: Mayte Gallego, Xu Bai, Kenso Soai, Stephen V. Frye, Lee F. Kuyper, Manoharan Muthiah, Michal Pietrusiewicz, Ernesto Brunet and Chen Xiangning.

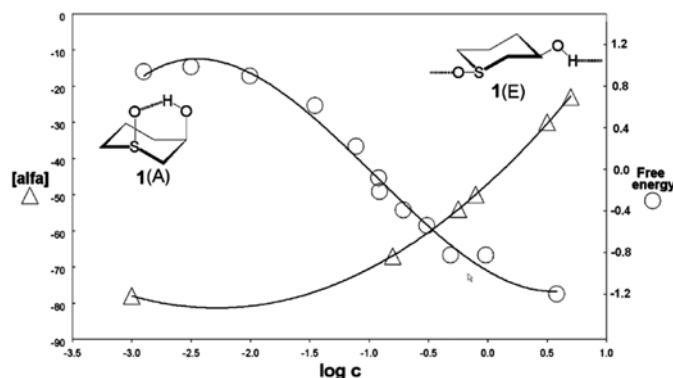
In previous work under Ernest's guidance some twenty years ago, we published on the unusual conformational behavior of *cis*-3-hydroxythiane S-oxide (**1** in Figure 4), a really simple molecule indeed [4].

Its NMR spectra in  $\text{CD}_2\text{Cl}_2$  at  $-70^\circ\text{C}$  showed that the diaxial conformer **1(A)** prevailed in dilute samples whereas at

high concentration the diequatorial conformation **1(E)** dominated. The only plausible explanation to this behaviour is a subtle balance between intra- and intermolecular hydrogen bonding interactions. In diluted samples entropy is against the gathering of two molecules and extra stabilization is achieved in the diaxial conformer by intramolecular hydrogen bonding between donor OH and acceptor SO groups. At higher concentrations, the probability of an encounter between two molecules increases and their association is more favourable when they are in the diequatorial conformation.

It should be noted that at the time of performing these experiments Ernest was already disturbed for a long time about the fact that key experimental evidence was missing concerning J.H. Brewster's suggestion that conformation and chiroptical properties should be strongly intertwined [5]. Ernest cleverly thought that *cis*-3-hydroxythiane S-oxide (**1**) would do the job of experimentally revealing that relationship once and for all. To that end, we synthesized the enantiomerically enriched molecule (ca. 60% e.e.) by Sharpless's oxidation of 3-hydroxythiane and measured its optical rotation in  $\text{CD}_2\text{Cl}_2$  at the range of concentrations tested by NMR. We found (Figure 4) a continuous variation of  $[\alpha]_D^{25}$  from -80 to -20 at high and low dilution, respectively, thus showing that the very same molecule did display a very different optical rotation depending on the preferred conformer. Moreover, a linear relationship was found between optical rotation and the population of axial or equatorial conformers leading to the equation  $[\alpha]_D^{25} = - (10.6x_E + 79.4x_A)$ , implying that specific rotation at any position of the conformational equilibrium is a weighted average of the specific rotation of the individual conformations.

To the best of our knowledge, the example of *cis*-3-hydroxythiane S-oxide is still the most clear-cut case in the literature concerning the relationship between conformation and chiroptical properties in solution. Although we did not realize it in the first place, the science behind these relatively simple experiments, dormant through many years, was actually the inspiration for our recent findings in the solid-state, where even larger qualms still remain in the understanding of chiroptical properties.



**Fig. 4.** Plot of  $[\alpha]_D^{25}$  (triangles) of compound **1** or  $\Delta G^\circ$  (circles) of the equilibrium between **1**(Axial) and **1**(Equatorial) vs. logarithm of its concentration in  $\text{CD}_2\text{Cl}_2$ .

## Results and Discussion

### Organic-inorganic materials based on $\gamma$ -zirconium phosphate

The controlled building of solid structures from bottom-up approaches is a challenging task. There are many successful lines of attack to this problem. Our conceptual toolbox, summarized in Figure 5, allows us to have a synthetic rationale, similar to that used in Organic Chemistry, to the preparation of solid structures. At the end of our retro-synthetic scheme is the gamma phase of zirconium phosphate ( $\gamma$ -ZrP) [6], the sustaining scaffold, which is a layered inorganic salt made out of two different kinds of phosphate groups: internal ones (green in Figure 5) bonded through their four oxygen atoms to four different zirconium metals; and external ones (blue in Figure 5) which bind two metals by means of only two oxygen atoms, the other two being OH groups which confer an acidic character to the surface. Therefore, organic bases can be easily intercalated and the sandwich maintained by ionic interactions. Furthermore, the external phosphates are amenable to topotactic exchange by phosphonates and other phosphorous functions under mild hydrothermal conditions, i.e. a reaction in which the surface phosphates are smoothly replaced without altering the layered structure of the inorganic salt. In principle, we may thus introduce within the layers of  $\gamma$ -ZrP any phosphonate with any conceivable organic function, whose properties will be modulated by their confinement in the inorganic matrix. Should the organic molecule bear phosphonate groups at both ends, the resulting material will be pillared and the inorganic layers will remain covalently linked [7].

The amount of topotactically exchanged phosphates may be easily controlled by simply adjusting the ratio of the reactants. Moreover, the remainder of the non-exchanged phosphates may be further replaced in a second topotactic reaction with a

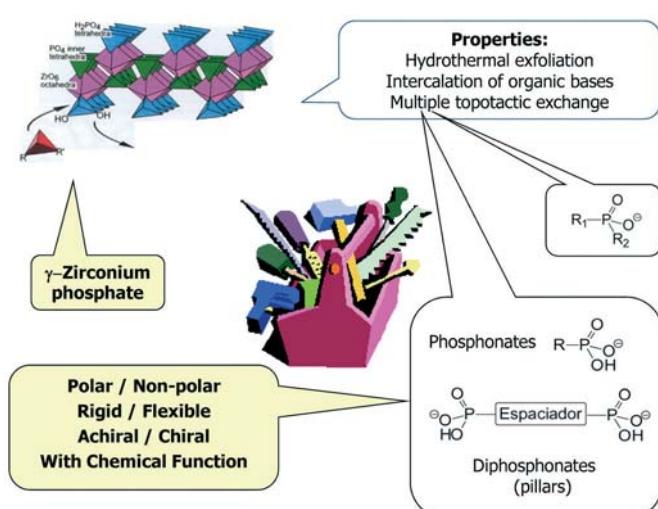
different phosphorous function. In this way, the solid structure can effortlessly be modified *a posteriori*, a task very difficult to perform in solid engineering. The use of the simple conceptual toolbox of Figure 5 has enabled us to prepare a series of materials with different properties and applicability. In the context of this paper, those derived from polyethyleneglycol or tartrate are of special relevance, as it will be explained shortly.

### Chiroptical properties of zirconium phosphate derivatives pillared with achiral columns

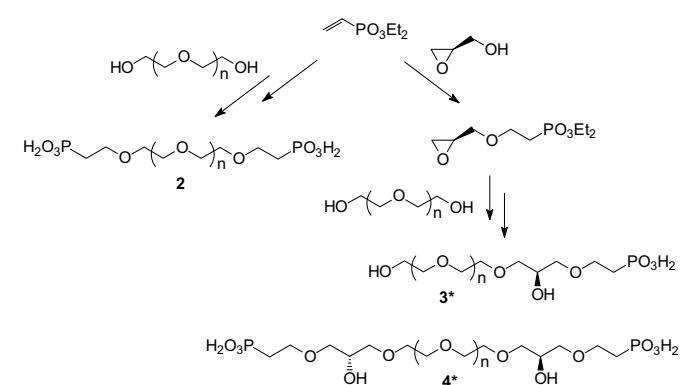
It was fairly easy to prepare achiral or chiral diphosphonates derived from polyethyleneglycol (Scheme 1). Their reaction with  $\gamma$ -ZrP in various conditions and the properties of the resulting microcrystalline solids have been reported elsewhere. To make a long story short, we will just state that powder x-ray diffraction studies of the methylamine-intercalated materials with achiral compounds **2** showed interlayer distances compatible with the coiled conformation of the polyethylenoxa columns (Figure 6), this finding also being supported by IR data [8].

Gian Lorenzo Bernini's High Altar at the Vatican's Basilica strongly reminds us of a portion of the material's idealized structure (Figure 6; methyl ammonium cations have been omitted). In fact, to a "stereochemistry-obsessed" observer, the view of the Altar, despite its rich ornamentation and cultural implications, leads to the appreciation of its "macroscopic" chirality due to the same handedness of the four curled columns. The very Altar in a mirror world would be non-superimposable upon the real one. It immediately occurred to us that the suggested helicity of the polyethylenoxa columns could be the source of "supramolecular" chirality, should the appropriate concourse of dissymmetric components be brought in. We thus achieved what we believe is the first example of chiral memory attained in the solid state.

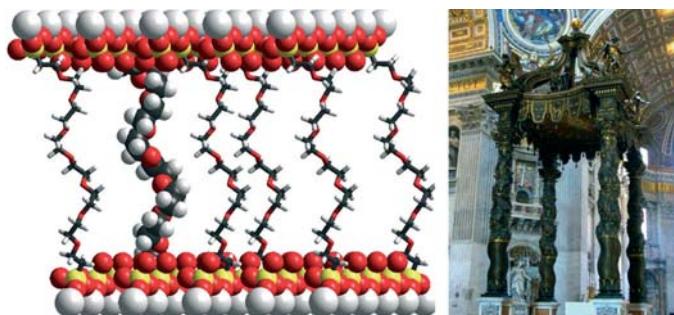
The most important experiments are summarized in Figure 7 and the details have been already published [9]. In short, the  $\gamma$ -ZrP phase exchanged at 25% with achiral hexaethyleneglycol diphosphonate (**2** in Scheme;  $n = 5$ ) was intercalated with optically pure (+)-1-phenethylamine [yellow ZrP-H25-PEA(+) in Figure 7]. Water dispersion of 5 mg of the resulting material in 10 mL of 1:1 water/acetone showed a reading of  $\alpha = 0.16$



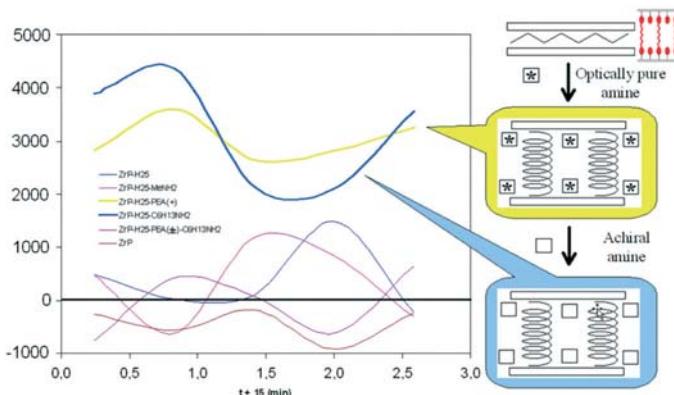
**Fig. 5.** Conceptual "tool box" for the building of organic-inorganic materials based on  $\gamma$ -ZrP, phosphonates and other phosphorous functions (see text).



**Scheme 1**



**Fig. 6.** Idealized molecular model of  $\gamma$ -ZrP topotactically exchanged with compound 2 (Scheme 1) at the interlayer distance measured in the methylamine intercalate by DRX (methylammonium cations are not shown); Gian Lorenzo Bernini's High Altar at the Vatican's Basilica.



**Fig. 7.** Specific optical rotation of suspensions of the indicated materials (see text).

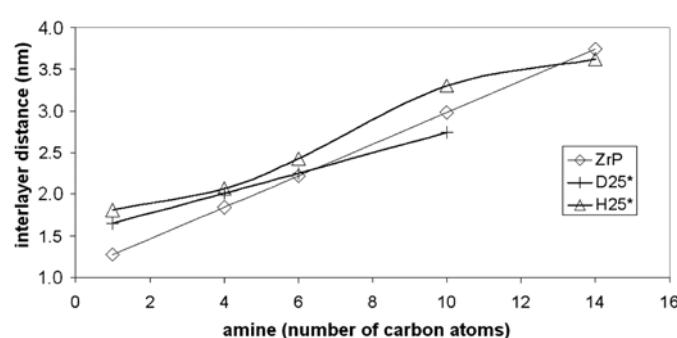
$\pm 0.06$  (the fluctuation is due to the inhomogeneity of the suspension) over 15 minutes. If it were a clear solution this value would correspond to a huge  $[\alpha]^{25}_D = +3400 \pm 1200$ . But, quite surprisingly, when we smoothly replaced PEA $^+$  by achiral hexylamine the optical rotation readings were maintained (blue ZrP-H25-C<sub>6</sub>H<sub>13</sub>NH<sub>2</sub> in Figure 7). The absence of PEA $^+$  was verified by NMR spectra. Additionally, we performed the necessary control experiments (Figure 7) showing zero-averaged optical rotation for the starting material (ZrP-H25), the same intercalated with methylamine (ZrP-H25-MeNH<sub>2</sub>) or racemic PEA and then hexylamine (ZrP-H25-PEA(±)-C<sub>6</sub>H<sub>13</sub>NH<sub>2</sub>). The absence of PEA $^+$  and the control experiments only left one possible source of optical activity in the material ZrP-H25-C<sub>6</sub>H<sub>13</sub>NH<sub>2</sub> with intercalated non-dissymmetric hexylamine: (PEA $^+$ )-induced deviation from the starting statistical 1:1 distribution of *P* and *M* helicity of the hexaethylenglycol columns that was retained when the chiral amine was replaced by the achiral one.

While the aforementioned experiments point to the scarcely-seen-so-far phenomenon of chiral memory in the solid state, Brewster's relationship between conformation and chiroptical

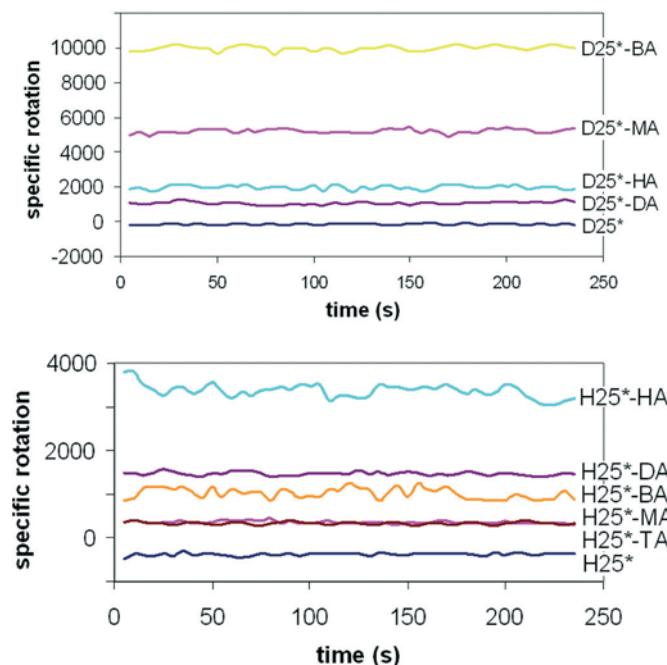
properties in the solid state had to be demonstrated with a different battery of experiments.

### Chiroptical properties of zirconium phosphate derivatives pillared with chiral columns

We first synthesized the enantiomerically pure mono- (**3\***) and diphosphonates (**4\***) of Scheme 1 and prepared the corresponding  $\gamma$ -ZrP phases exchanged at ca. 25% (the details were given elsewhere) [10]. The acronyms **D25\*** and **H25\*** stand for the materials made from the diphosphonates of di- ( $n = 1$  for **4\*** in Scheme 1) and hexaethylenglycol derivatives ( $n = 5$  for **4\*** in Scheme 1), respectively. **DM25\*** represents the material prepared from the monophosphonate of the diethylenglycol derivative ( $n = 1$  for **3\*** in Scheme 1). In all cases, the number in the acronym is indicative of the phosphate/phosphonate exchange level.



**Fig. 8.** Plot of interlayer distance as measured by DRX vs. the number of carbons of the intercalated amine for the indicated materials.



**Fig. 9.** Specific rotation along 3 min of the indicated materials (see text).

We then proceeded to intercalate simple alkylamines of different length in order to progressively increase the interlayer distance as measured by powder XRD (Figure 8). As it was earlier seen, the longer the chain length of the amine the larger the interlayer separation in native  $\gamma$ -ZrP. In the case of **D25\*** the slope was lower thus showing a certain resistance for the layers to be separated. For **H25\*** the variation was sigmoid, i.e. the layers were more difficult to be detached of each other either with the shortest or with the longest amines.

The optical rotation of each intercalate was measured following a strict protocol (sonication for 10 min, standing for 15 min, a measured every 5 s for 3 min) from dispersions of 5 mg of the material in 10 mL of 1:1 water-acetone. Figure 9 shows as an example the results for **D25\*** and **H25\*** intercalated with methyl- (MA), butyl- (BA), hexyl- (HA), decyl- (DA) and tetradecylamine (TA).

The plot of Figure 10 summarizes the variation of optical rotation vs. amine length for **D25\***, **H25\*** and **DM25\***. It may be seen that the basal spacing continuously increased vs. amine length but, interestingly, optical rotation did not. In the case of the **D25\*** and **H25\***, optical rotation reached a maximum corresponding closely to the intercalation of butyl- and hexylamine, respectively. In the case of the monophosphonate (**DM25\***), the curve reached a plateau further on from butylamine.

At this point the reader should remember that the inorganic layers are covalently bonded in the instance of the diphosphonates but, with the monophosphonate, they are loose. By fixing the experimental interlayer spacing induced by the corresponding intercalated amine, molecular modelling shows that the intrinsically chiral ethylenpolyoxa chains of the diphosphonate should adopt different conformations (Figure 11). With short amines, the models suggest the chains are compressed and disordered between the layers. With longer amines, the chains have to adopt an increasingly stretched conformation, ending up in a nearly perfect zigzag arrangement. In the case of **H25\***, the model with the experimental interlayer distance of hexylamine shows that the ethylenpolyoxa chains may adopt the conformation of very relaxed coils, thus maximizing its possibilities of expressing chirality. Surely not by chance, the highest optical rotation of **H25\*** was observed at this very point, the only plausible explanation to it being the predominance of helix conformations in *P* or *M* form. Disorder and compression on one hand or stretching on the other (with shorter and longer intercalated amines, respectively) makes the coiling to be imperfect or impossible, correspondingly. It thus makes sense that optical rotation was smaller at short and large interlayer distances. It is also quite significant that **D25\***, with shorter pillars than **H25\***, attained the maximum rotation in the butylamine intercalate, i.e. with a shorter amine too (cf. Figure 10).

We believe that the pre-existing stereocenters of the diphosphonates constrained the manner in which they were attached to the inorganic layers at the precise moment the material was created. Molecular mechanics calculations performed on **3\*** ( $n = 5$ ; cf. Scheme 1) either in *vacuo* or under

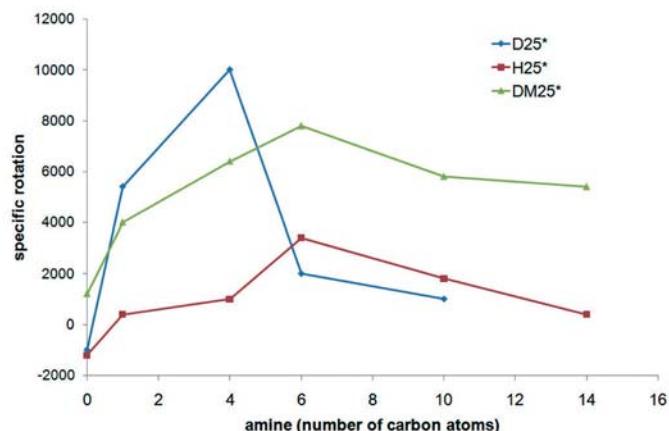


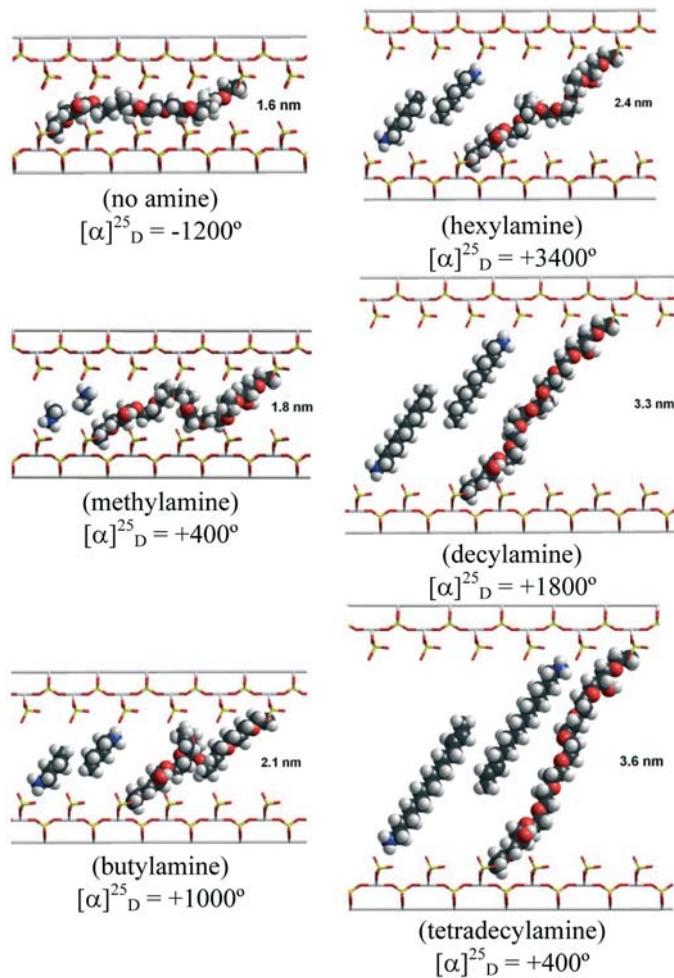
Fig. 10. Plot of  $[\alpha]_D^{25}$  vs. the number of carbons of the intercalated amine for the indicated materials.

the influence of ca. 350 molecules of water suggested that the *M* configuration might be more stable by 1.4 (*vacuo*) or 13.0 (water) kcal/mol than its *P* counterpart. Therefore, it is plausible that the handedness of the coiling be predestined from the start. Additional experiments are underway to check these assumptions but, regardless of their outcome, we believe that the described results have already shown that *Brewster's principle of interrelation between conformation and chiroptical properties is also relevant for microcrystalline, layered solids*.

The behavior of the monophosphonate intercalates (**DM25\***) reinforces this conclusion (cf. Figure 10). In this case, the inorganic layers are not covalently bonded whatsoever. Yet, the possible coiling of the organic chains must be also disturbed by compression and disorder when the lamellae are scarcely separated either because there is no intercalation or short amines are intercalated. Nevertheless, with amines of sufficient length, the coiling can be freely expressed and, since the monophosphonate chains are only attached by only one end to the inorganic phase, a longer amine cannot produce chain stretching. Coiling cannot thus be destroyed by the longer amines as it certainly was in the case of the pillared **D25\*** and **H25\*** examples. This is compatible with the experimental observation of a large, nearly constant value of optical rotation from butyl- to tetradecylamine (Figure 10).

#### Attempts of achieving enantioselective molecular recognition

One of the most important challenges of modern organic, inorganic and analytical chemistry is the synthesis of microporous solids that selectively and reversibly enclose certain analytes. In recent years, layered metal phosphates and phosphonates have received considerable attention because the structures of these zeolite analogues can be tailor made at will. In terms of shape selectivity, enantioselective recognition from a racemic mixture is significantly more demanding than the detection of achiral molecules. Both enantiomers possess identical chemi-



**Fig. 11.** Calculated most stable conformation of a single column  $4^*$  (Scheme 1) attached to  $\gamma$ -ZrP (material H25\*) for the different interlayer distance (nm) induced by the corresponding intercalated amine shown.

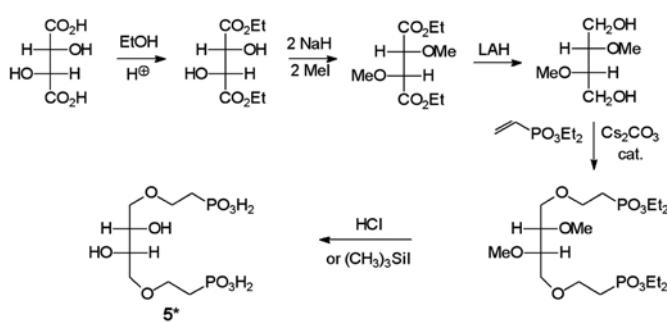
cal functions and have to be resolved by multipoint binding to a chiral host following the lock-and-key principle. We reasoned that the pores within our chiral scaffolds could perform this function. Table 1 lists the results of the materials used to perform enantioselective molecular recognition experiments. The descriptors **D25\*** and **H25\*** have already been defined, and the acronyms **TARn\*** refer to  $\gamma$ -ZrP exchanged to  $n$  % with the diphosphonates **5\*** derived from enantiomerically pure tartaric acid as shown in Scheme 2.

We have selected PEA as the guest molecule, due to its simplicity and inexpensive availability as racemate or enantiomerically pure forms. Besides, the e.e. can be quickly and accurately measured by GC with the appropriate chiral stationary phase. We thus designed two different groups of experiments: one under thermodynamic conditions and the other group to qualitatively determine the kinetics of the recognition process.

In the first group we attempted to realize chiral recognition by means of the intercalation of the racemic amine into

**Table 1.** Enantiomeric excess measured in the mother liquors of the suspension of the indicated materials with  $(\pm)$ -PEA (see text).

Product	e.e. (isomer)		PEA content per Zr
	24 h	48 h	
<b>D25*</b>	2.3 ( <i>R</i> )	2.2 ( <i>R</i> )	0.80
<b>H25*</b>	3.1 ( <i>S</i> )	2.5 ( <i>S</i> )	0.90
<b>TAR25*</b>	5.9 ( <i>S</i> )	8.0 ( <i>S</i> )	0.92
<b>TAR35*</b>	7.5 ( <i>S</i> )	11.7 ( <i>S</i> )	0.80
<b>TAR70*</b>	11.5 ( <i>S</i> )	14.1 ( <i>S</i> )	0.25



**Scheme 2**

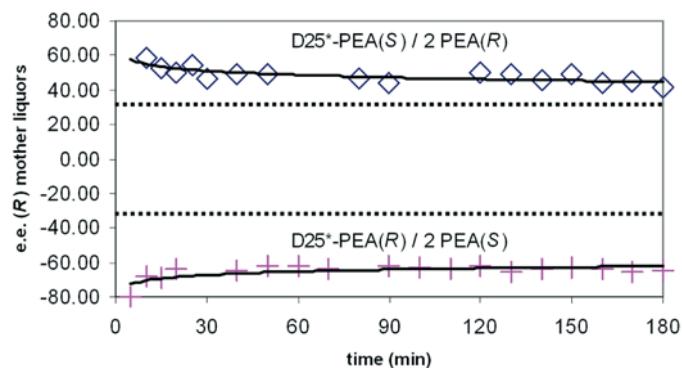
the chiral material. Should recognition take place, one enantiomer would predominantly intercalate versus the other, thus leading to a measurable e.e. in the mother liquors. To accomplish that, the solid materials were suspended in a 0.02M solution of  $(\pm)$ -PEA containing 2 eq of amine per eq of Zr. Aliquots of the mother liquors were analyzed by GC (*vide supra*) after 24 and 48 h and Table 1 lists the final results (further variations in e.e. were not observed after 48 h). Unfortunately, enantiomeric recognition was very small. The long diphosphonates derived from di- and hexaethylenglycol (see Scheme 1) showed the lowest degree of enantioselective recognition. The TAR materials, derived from tartaric acid (Scheme 2), exhibited a sizeable recognition for the *R*- $(+)$ -PEA isomer since its mirror-image isomer was found to be enriched in the mother liquors. In general, the higher the diphosphonate content of the material, the larger the observed recognition. Table 1 also displays the amine content of the resulting PEA-intercalated material of each experiment. It may be seen that all solids ended up with approximately one amine per remaining acidic phosphate. XRD analysis of these materials showed in general broad peaks (low crystallinity) but, in average, an interlayer distance of 2.1 nm was measured, very similar to the basal spacing of pristine  $\gamma$ -ZrP intercalated with a double layer of PEA (2.15 nm). In the case of the TAR derivatives, this interlayer distance is close to the maximum possible calculated by molecular modelling (2.3 nm) for the most extended confor-

mation of TAR columns. Therefore, it should be assumed that for PEA-intercalated **TAR70\***, the sample showing the highest enantiomer recognition, there is also a double layer of amines in the scarce space left among the almost fully extended tartrate-derived columns. The highest preference for the *R* isomer of PEA was attained in this case where the amines should be in the closest possible contact with the tartrate columns. The higher proximity of the stereocenters to the phosphonate end of the chain in the TAR derivatives as compared to those derived from glycidol (Scheme 2) and the higher abundance of chains in **TAR70** should make the void spaces more shape demanding to the host PEA isomer. The e.e. obtained for **TAR70\*** is very promising in order to use this material as a stationary phase for chromatographic separations where the lock-and-key interactions should be magnified.

The second type of experiment consisted of preparing two different binding phases, each of them enclosing one of the pure PEA enantiomers. These solids were suspended and stirred at room temperature in an aqueous solution which contained two eq of the opposite enantiomer. By means of the e.e. evolution in the mother liquors over a period of time, it was possible to determine the rate at which the two enantiomers exchanged places from the interior of the solid material into the mother liquors (and *vice versa*). This enabled us to study whether one of the enantiomers was accommodated within the chiral cavities faster than the other, *i.e.* whether or not the binding phases were capable of exerting kinetic chiral recognition. This is a competitive experiment, in which one enantiomer replaces the other previously accommodated inside. Thus, it was necessary to run independent assays with both enantiomers inside/outside in order to ascertain that the results were complementary, in the case some kinetic recognition exists. We decided to use **D25\*** which showed very little if at all thermodynamic recognition (Table 1).

Figure 12 shows the variation of e.e. over time in the mother liquors for **D25\*-PEA(S)** and **D25\*-PEA(R)** during 3 h. The dashed lines indicate the equilibrium situation (2:1 or  $\pm 33.3\%$  e.e.), equivalent to a lack of chiral recognition, in which the PEA(*S*)-to-PEA(*R*) ratio would be the same inside and outside the material. To our surprise, these levels were never reached. First of all, it should be noted that the in-out flux of amines was relatively fast because after the first 5 min the e.e. of the mother liquors was very far from the initial expected  $\pm 100\%$ . This is seen by the e.e. reduction to 55% of PEA(*R*) in the mother liquors (ML) after the first 5 minutes of incubation when starting with **D25\*-PEA(S)**, whereas the e.e. decrease was reduced to only 20% of PEA(*S*) in the ML during the same period when starting with **D25\*-PEA(R)**. This suggests that PEA(*S*) is faster in leaving and slower in entering the chiral matrix than its PEA(*R*) counterpart.

At the end of the experiment (3 h) e.e.'s were 45% and -60% from **D25\*-PEA(S)** and **D25\*-PEA(R)**, respectively, quite far from the  $\pm 33.3\%$  indicative of no recognition. In other words, after 3 h, 1eq of pure **D25\*-PEA(S)** suspended in a solution of 2eq of pure PEA(*R*) ended up with a 0.55:0.45 *R/S* ratio within the solid, whereas 1eq of **D25\*-PEA(R)** sus-



**Fig. 12.** Variation of e.e. for *R* enantiomer of PEA over time for the dispersions of **D25\*-PEA(S)** and **D25\*-PEA(R)** in a 1:1 water acetone solution of the corresponding opposite enantiomer (see text).

pended in a solution of 2eq of PEA(*S*) gave a 0.60:0.40 *R/S* ratio within the solid. Therefore, in the longer run of 3 h, the PEA(*S*) isomer showed a tendency to leave the inside of the solid host. On the other hand, the PEA(*R*) was quite reluctant to depart from the organic-inorganic host. These facts clearly show that PEA(*R*) is more stable than its enantiomer within **D25\*** and that the chiral solid matrix displayed a kinetic and thermodynamic recognition towards PEA(*R*) which was not evident from the experiments with the racemate (*vide supra*).

There is a relatively simple explanation to these apparently contradictory results. When the material **D25\*** was treated with racemic PEA a negligible enantiomeric recognition was observed (Table 1). The initially deflated volume matrix, with no pre-existing conformational preference of the **3\*** columns ( $n = 1$ ; Scheme 1), expands to accommodate a double layer of racemic PEA. It is not possible to know whether the two enantiomers enter the same interlayer gallery or not. However, when **D25\*** is treated with either PEA(*R*) or PEA(*S*) the chiral columns have the chance to express in full a particular conformation to best house the specific handedness of the amine. As a consequence, two supramolecularly diastereomeric composites are formed which should differ in energy. The fact that PEA(*R*) was more reluctant to exit the solid matrix would suggest that **D25\*-PEA(R)** is the most stable diastereomeric entity and that there seems to be a better complementary *matching* between the conformation/configuration of the chiral columns and PEA(*R*).

## Conclusion

The work on *cis*-3-hydroxythiane *S*-oxide (**1**) performed under Ernest's guidance clearly demonstrated Brewster's hypothesis that conformation and chiroptical properties are closely intertwined. Our simple dilution experiments showed that, despite the fact that the two conformers of **1** obviously share the same configuration at their stereocenters, they displayed very different specific optical rotation, thus showing that the

overall arrangement of the molecule is what actually matters concerning chiroptical properties. After many years, our research endeavours with chiral organic-inorganic materials ultimately were fruitful. We have shown that the conformation of intrinsically chiral organic moieties can be heavily altered at the supramolecular level within a solid matrix, determining striking differences in the measured values of specific optical rotation. Brewster's assumption has thus been expressed in the solid state, in the new field of organic-inorganic composites. Very preliminary results of these findings were presented at the symposium honoring Prof. Eliel within the 2004' ACS 56th Southeast Regional Meeting. This symposium was far too modest in recognizing Eliel's outstanding contributions to Chemistry and to society as a whole.

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