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# Implications of flexible spacer rotational processes on liquid crystal behavior of 4,5-dihydroisoxazole benzoate dimers

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The synthesis of some novel non-symmetric liquid crystal dimers {3-[4-(octyloxyphenyl)]-4,5-dihydroisoxazol-5-yl}alkyl 4-(decyloxy)benzoates (**5a-d**) and 4-{3-[4-(octyloxyphenyl)]-4,5-dihydroisoxazol-5-yl}alkyl 4-{[6-(octyloxy)naphthalen-2-yl]ethynyl}benzoate (**9a-d**) are reported. The liquid-crystalline properties, theoretical calculations based on the conformational issue of the alkyl flexible spacer and X-ray experiments are discussed. The synthesis of key intermediate 2-{3-[4-(octyloxy)phenyl]-4,5-dihydroisoxazol-5-yl}alkanol (**3a-d**) carrying on the alkyl flexible spacer were done by [3+2] cycloaddition reaction between nitrile oxides, which were generated *in situ* by oxidation of respective aromatic oximes, and dipolarophiles alkenol ($CH_2$=CH($CH_2$)$_n$OH, *n* = 1, 2, 3, and 4). Benzoates **5a-d** were synthesized through esterification of **3a-d** and *p-n*-decyloxybenzoic acid (**4**). Esters **9a-d** were synthesized by derivatization of isoxazolines **3a-d** into 4-{3-[4-(octyloxyphenyl]-4,5-dihydroisoxazol-5-yl}alkyl 4-bromobenzoate (**7a-d**) followed by Sonogashira reaction with 2-ethynyl-6-octyloxynaphthalene (**8**). **5a** and **5b** showed monotropic smectic C phase. **9a/c** displayed enantiotropic nematic (N) mesophase, whereas **9b/d** showed monotropic nematic mesophase No mesophase was observed to **7a-d**. An odd-even effect was observed for **5a-d** and **9a-d** associated to the crystal to isotropic phase transition and crystal to nematic phase, respectively as the length of the spacer is moved up from 1 to 4 carbon atoms. The X-ray data of compounds **5a** and **5b** are in agreement with polarizing optical microscopy observations with the assignment of SmC mesophase. Density functional theory calculations using the B3LYP hybrid functional at level 6-311G(d,p) basis set were performed for molecules **5a-d** to correlate the conformation of the flexible spacer and the transitional properties. The conformational analysis showed that the most stable conformation for **5a-d** is one that where all the carbon atoms of the flexible spacer are orientated at 180° (*antiperiplanar* orientation) except for the **5a** because the spacer is too short. The odd members are more bent-shape and less elongated molecule than for even members. Thus, mesomorphic behavior is dictated by the conformational constraint imposed by the flexible spacer to the mesogenic groups.

## Introduction

Liquid crystal oligomers (LCO) are a special class of soft materials being formed by two or more anisotropic-shaped cores connected by flexible spacers, normally alkyl chains.[1] The core is usually a mesogenic group and the simplest LCO is termed the dimers and it has just two mesogenic units linked chemically to a single methylene chain.[2] The first report about liquid crystal dimers was made by Vorländer[3] at the beginning of the 20s and by Rault[4] some years later. However, these important reports appear to have been forgotten in some place of the past until the early of 1980s, when they have been rediscovered again and gained a new dress.[5] The LCO are composed in their vast majority by two symmetric rod-like mesogenic units,[6] whereas their non-symmetrical analogues[7] have two different mesogenic groups connected by a flexible alkyl chain and less frequently by oligo(ethyleneoxide),[8] oligo(siloxane)[9] and sulfur-sulfur link[10] in the chain. In this context, length and parity of the flexible spacer are important parameters that have a great influence on the transitional properties.[11] Dimers and higher oligomers, such as trimers[12-14] and tetramers,[15-16] have special level of attention due to their ability to act as model compounds for semi-flexible main-chain liquid crystal polymers.[17-18] Also, from the academic point of view these oligomers are interesting because they behave differently to that of conventional liquid crystals of low molar mass.[19-20]

The mostly LCO have an aryl group as mesogenic unit and few examples of LCO incorporating 5- and 6-membered rings such as 1,3,4-oxadiazoles and pyridyl-based dimers respectively, have also been published, with their transitional properties being investigated.[21-22] Compounds containing a 4,5-dihydroisoxazole moiety have been prepared recently and the liquid crystalline behavior evaluated.[23] To the best of our knowledge, however, there have been no examples of non-

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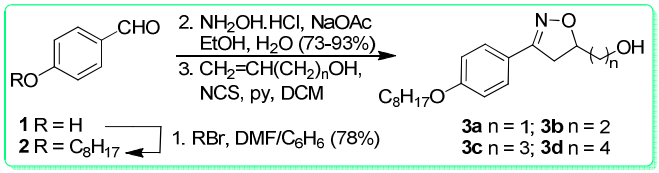
symmetric 4,5-dihydroisoxazole-based liquid crystal dimers reported in the literature.

We have previously reported[24] the synthesis of liquid-crystalline 3,5-disubstituted isoxazolines, where of the number of carbon atoms of the terminal aliphatic chains exerts a strong influence on the molecular shape and mesomorphic behavior. In this work, we report the synthesis and transitional properties of two new homologous series of non-symmetrical liquid crystal dimers 3,5-disubstituted 4,5-dihydroisoxazole benzoates with emphasis on the dependence of the liquid-crystalline transition temperatures on the number of methylene carbon atoms of flexible spacer. Density functional theory (DFT) calculations combined with X-ray analysis supported this study.

## Results and Discussion

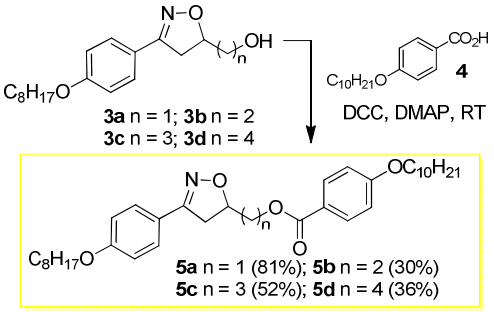
### Synthesis and Liquid-crystalline behavior description

The synthetic route used for the preparation of the isoxazolines **3a-d** is shown in Scheme I. We selected the aldehyde **2** as a precursor for reactive arylnitrile oxide.[25] Thus, the aldehyde **2** was synthesized from alkylation of 4-hydroxybenzaldehyde **1** with octylbromide in 78% yield. The isoxazolines were obtained by [3+2] 1,3-dipolar cycloaddition[26] of nitrile oxide from in situ oxidation reaction of 4-octyloxybenzaldehyde oxime and four different dipolarophiles from alkenol - $CH_2$=$CH(CH_2)_n$OH, *n* = 1, 2, 3, and 4. The final key isoxazolines **3a-d** were obtained in low yields (33-36%).




**Scheme I.** Synthetic route used to prepare the compounds **3a-d**.

The design and synthesis of the liquid crystals **5a-d** and **9a-d** were based on creating the structural characteristics necessary for the occurrence of a mesophase through a short and quickly synthesis. Thus, the first homologous series **5a-d**, (Scheme II) were prepared by the esterification of the compounds **3a-d** and 4-*n*-decyloxybenzoic acid **4** in the presence of DCC and catalytic amounts of DMAP in a THF solution at room temperature. The compounds **7a-d**, prepared from the esterification reaction between the compounds **3a-d** and 4-bromobenzoic acid **6** in the presence of DCC and catalytic amounts of DMAP in THF, are precursors for the synthesis of the liquid-crystalline materials **9a-d**. The yield reported for the compounds **5a-d** and **7a-d** refer to the pure compounds after purification process by recrystallization or chromatography column to remove the undesirable byproduct urea.




**Scheme II.** Preparation of dimers 3,5-disubstituted 4,5-dihydroisoxazole benzoates **5a-d**.

The compounds **9a-d** were prepared using a Sonogashira cross-coupling reaction between the intermediates **7a-d** and the terminal alkyne **8**[27] in the presence of palladium catalyst, i.e., $(PPh_3)_2PdCl_2$, CuI, $PPh_3$ in $NEt_3$ (Chart I).

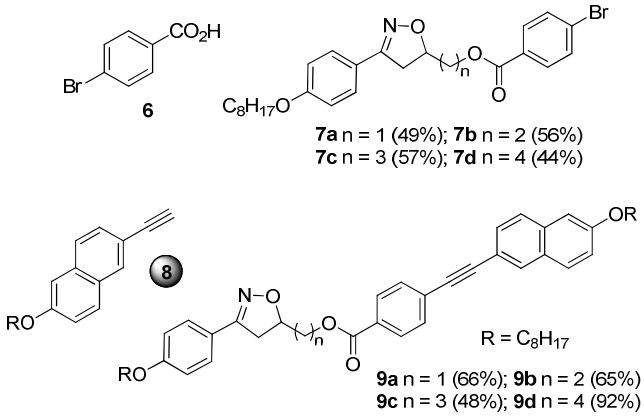



**Chart I.** Intermediates and final compounds of the series **7a-d** and **9a-d**.

The mesophase identification for the LC compounds **5a-d** as well as for the **9a-d** was made by polarizing optical microscopy (POM). The smectic C mesophase (SmC) was assigned by the observation of a typical broken fan texture (at the top of Figure 1 (a) for **5a** and *schlieren* texture (at the bottom of Figure 1 (c) for **9b**. For compound **5b,** the mesophase SmC range was very narrow and it appears very quickly before that the crystallization takes places [Figure 1 (b)]. The DSC traces for **5b** display a peak related to the transition temperature of the crystal phase to isotropic phase. The SmC mesophase for **5c** and **5d** was detected and the texture persists for just few seconds followed by fast crystallization. No pictures in the POM neither shoulders in the DSC traces for these compounds could be acquired. Identification of the nematic mesophase for compounds **9a-d** was made from the observation of typical *Schlieren* texture with two- and four-point brushes and planar texture [Figures 1 (c) and (d)]. The low enthalpy valuesassociated with transition of the nematic mesophase to isotropic state corroborate with this assignment (Table 1).

Compounds **5a-d** are composed by two terminal alkyl chains - eight carbon atoms on the isoxazoline side and ten carbon atoms on the ester side. The variation was made on the

number of carbon atoms in the flexible spacer. So, **5a-d** have n = 1, 2, 3, and 4 in the flexible spacer, respectively.

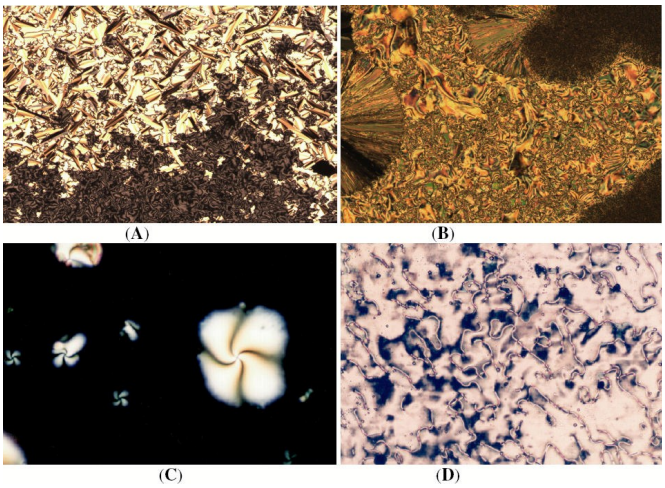



**Figure 1.** Photomicrographs of the textures obtained by optical microscopy on cooling (x10) of: (A) the broken fan texture (at the top) and *schlieren* texture (at the bottom) of SmC mesophase displayed by the compound **5a** below 79 °C, (B) coexistence of broken fan texture of SmC mesophase and crystal phase displayed by compound **5b** below 58 °C in fast cooling, (C) Schlieren texture of the nematic mesophase displayed by the compound **9b** below 129 °C, (D) Thread-like texture of the nematic mesophase displayed by the compound **9d** below 120 °C.

The transition temperatures showed in Table 1 were obtained by combination of POM and DSC analysis. Compounds **5a** and **5b**, upon second cooling cycle exhibit a monotropic phase with two exothermic peaks at 83 °C and 61 °C, respectively. These peaks were associated to the transition temperature when the samples enter into SmC mesophase from isotropic state. Upon further cooling, **5a** and **5b** displayed crystallization peak from the SmC mesophase, at 74 °C and 54 °C, respectively. To the higher homologous **5c** and **5d**, DSC traces have showed only peaks related to crystal phase to isotropic phase transition. However, samples of **5c** and **5d** when analyzed by POM upon fast cooling, displayed a monotropic SmC phase before recrystallization. For compounds that belong to the homologous series **9a-d** the terminal alkyl chains was fixed at eight carbon atoms (*n*-octyl). The variation in the flexible spacer was made in the same way as describe for **5a-d**. According to the DSC data [Table 1, Figures 1(c) and 1(d) and Fig S31 (ESI)], **9a** and **9c** homologues of this series exhibit an enantiotropic nematic mesophase, while **9b** and **9d** display a monotropic nematic mesophase. Upon heating, the temperature range decreases by increasing the number of methylene units in the aliphatic chain, e.g., for **9a** $\Delta T$ = 13 °C and for **9c** $\Delta T$ = 9 °C. For **9b** and **9d**, a monotropic nematic mesophase was observed being more persistent to **9d**, whereas **9b** displayed nematic mesophase for a few seconds by quick cooling from the isotropic state to room temperature. Under this circumstance the nematic mesophase grow up along with crystals formation.

The compounds **9a-d** have a more pronounced rod-like, lath-like structure than compounds **5a-d** and **7a-d** and, consequently, they exhibit enantiotropic mesophase at higher temperatures that those of compounds **5a-d**.

Melting point for **5a-d**, **7a-d** and **9a-d** displayed an odd-even effect as the length and parity of the flexible spacer is varied. The values of the melting point alternates as the length of the flexible spacer chain increases with odd members exhibiting the higher values. The alternation is attenuated by increasing the spacer length. Values of the entropy associated with the melting point of **5a-d** displayed the odd-even effect while **9a-d** did not follow the tendency observed for **5a-d** probably due to the nature of mesophase that accompanying the crystal phase (Figure 2).

**Table 1.** Liquid-crystalline transition temperatures (° C)*, enthalpy and entropy values (kcal mol$^{-1}$) for the homologous series **5a-d**, **7a-d,** and **9a-d**.

| Entry | Transition phase temperatures | | $\Delta T^d$, °C | Enthalpy, $\Delta H$ | | Entropy, $\Delta S/R^f$ |
|---|---|---|---|---|---|---|
| | Heating | Cooling | | Melt$^e$ | I - phase – Cr | |
| **5a** | Cr 103 I | I 83 SmC 74 Cr | 9 | 17.9 | I 3.1 SmC 10.4 Cr | 24.0 |
| **5b** | Cr 72 I | I 61 SmC 54 Cr | 7 | 8.7 | - | 12.5 |
| **5c** | Cr 85 I | I 66 Cr$^b$ | - | 23.0 | - | 32.4 |
| **5d** | Cr 68 I | I 57 Cr$^b$ | - | 13.4 | - | 19.5 |
| **7a** | Cr 115 I$^a$ | I 104 Cr | - | - | - | - |
| **7b** | Cr 90 I$^a$ | I 77 Cr | - | - | - | - |
| **7c** | Cr 99 I$^a$ | I 81 Cr | - | - | - | - |
| **7d** | Cr 73 I$^a$ | I 61 Cr | - | - | - | - |
| **9a** | Cr 150 N 163 I | I 162 N 136 Cr | 13 | 13.0 | I 0.4 N 13.2 Cr | 15.4 |
| **9b** | Cr 130 I | I N$^c$ 120 Cr | - | 10.0 | I 10.5 Cr | 12.4 |
| **9c** | Cr 136 N 145 I | I 144 N 126 $Cr_1$ 116 $Cr_2$ | 9 | 9.3 | I 0.9 N 0.8 $Cr_1$ 8.5 $Cr_2$ | 11.5 |
| **9d** | Cr 130 I | I 122 N 112 Cr | 10 | 12.7 | I 0.5 N 11.5 Cr | 15.8 |

*Onset temperatures ($T_{onset}$). Data obtained from DSC (2$^{nd}$ cycle) with rate of heating and cooling of 10 °C min$^{-1}$; Cr = crystal phase, SmC = smectic C mesophase, N = nematic mesophase, I = isotropic liquid. $^a$Temperatures were obtained by optical microscopy. $^b$SmC or $^c$N mesophases were observed only on fast cooling - samples were exposed to room temperature. $^d$Mesophase range upon cooling for compound **5a-b** and **9d** and upon heating for **9a** and **9c**. For **9b** the temperature range was too small to be measured. $^e$Enthalpy values (second cycle heating/cooling) obtained in the Cr – I transition for the series **5a-d** and Cr – N transition for the series **9a-d**. $^f$Values of melting entropy obtained in the Cr – I transition for the series **5a-d** and **9b/d** and Cr – N for **9a/c**. R = 8.31 J K$^{-1}$ mol$^{-1}$.

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For homologous series **9a-d** the odd-even effect based on mesomorphic behavior is also barely observed upon cooling samples from isotropic phase. A stable nematic mesophase was observed for **9a** and **9c**, however, for **9b** and **9d** the nematic mesophase are only visible during the cooling cycle. **9b** displayed N mesophase upon cooling with very short period of time [Figure 1(c)]. Upon cooling, all samples showed a nematic mesophase. The correlation between length and parity of the flexible spacer is not an easy task to do considering that upon heating **9b** and **9d** did not display mesomorphic behavior. Naphtyl group connected by triple bond to the benzoate moiety induce the formation of stable mesophase when compared to the series **5a-d**. However, a conformational issue associated to the flexible spacer alters the molecular packing in the mesophase, and consequently induce a dependence of intermolecular interaction between aromatic ring and size of flexible spacer. When we move along the carbon skeleton of flexible spacer, the aromatic rings rotate around the last carbon bond to produce a set of distinct conformations to **9a/c** and **9b/d**. Obviously, transitional properties analysis in this article suffers a drawback because the nematic phase behavior is only stable for **9a** and **9c**. However, melting point upon heating or cooling exhibit an even-odd effect as showed in Fig. 2 for **5a-d** and **9a-d** series. The odd members displayed higher values of melting point than even members.

Dependence of the entropy changes associated with the crystal–isotropic transition on the number of methylene units (*n*) present in the flexible spacer of non dimeric LC **9a-d** does not follow a regular tendency due to the nature of nematic phase observed in this series of liquid crystals (Fig 2, bottom). Anyway, it is possible to state that the differences between odd and even membered dimers reflect, at least, the difference in their average molecular shapes, which are governed in a large extent by the parity of the flexible spacer.[1]

Transitions from more ordered mesophase to isotropic state have more entropy than transition between disordered phase to isotropic state. The less ordered phases, such as nematic phase, display lower entropy value and consequently, when they undergo to isotropic liquid state are less sensitive to structural parameters, such as variation on the flexible spacer, due to the absence of short- or long-positional order of the molecules.

A bar graphics is also presented for all compounds **5a-d** and **9a-d** in this study to get a better view of the odd-even effect. Figure 2, at top, represents the melting point for **5a-d** and transition temperatures upon heating for **9a-d**. At bottom of Fig. 2, a plot of entropy values for Cr → I for **5a-b** and Cr → N for **9a-d** (ΔS/R) is showed.

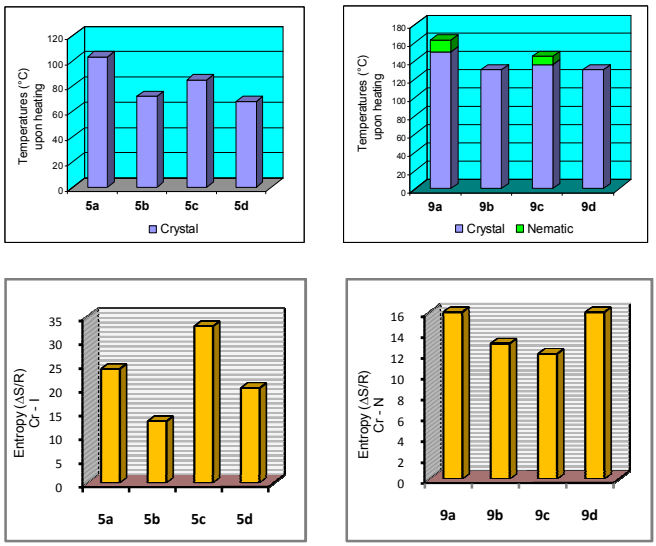


**Figure 2.** Bar graphics for **5a-d** and **9a-d**. Plot of temperatures (°C) upon heating (top) and entropy values for Cr → I for **5a-b** and Cr → N for **9a-d** (ΔS/R) (bottom).

### Theoretical calculations

Theoretical calculations were performed to evaluate the influence of the number of methylene carbon atoms in the flexible spacer chain on the most stable conformation of the compounds of the series **5a-d**. DFT calculations were carried out in order to obtain the optimized geometries and conformational distributions for the molecules **5a-d**. All the calculations were done with Gaussian 03[28] computational package and the geometries was optimized in vacuum using the B3LYP[29] hybrid functional at level 6-311G(d,p) basis set. In order to compare the energies, geometries and dipoles moments with the ones obtained in gas phase, **5a** structure was calculated using PCM model as solvent effect and water and cyclohexane as solvent with high and low dielectric constant, respectively.[30] Calculations were performed considering that the molecular shape having a prominent effect in liquid crystal behavior is primarily determined by the rotational process.[31] The study here is guided by the fact that **5a-d** and **9a-d** containing a five-membered heterocyclic ring, named $\Delta^2$-isoxazolines are connected to a benzoate moiety core by a flexible aliphatic spacer. The spacer in liquid crystal dimers contribute to the molecular anisotropy and exert a control of the relative orientation of the two mesogenic groups.

The $\Delta^2$-isoxazolines presents a non-traditional bent-shape as consequence of tetrahedral carbon atoms, $C_4$ and $C_5$ in the heterocyclic ring. Deviations from linearity as well as the non-coplanarity of aryl groups bonded to $C_3$ and $C_5$ of isoxazoline

have a pronounced influence on the mesophase formation as well as on the liquid crystal mesophase stability. To compensate this geometrical constrains, the elongating molecular strategy is applied for. Previous results has shown that stable mesophase formation is reached when high anisotropic group are linked to $C_3$ and $C_5$ of isoxazoline carbon atoms.[24]

For mesogens composed of flexible molecules a large number of conformational states can be obtained due to arrangement antiparallel or inclined for odd and even dimers and degrees of freedom related to the alkyl chains. In fact, calculations performed in this work showed a set of lowest energy conformation to **5a**-**d** with energy barrier lower than 1.0 kcal.mol$^{-1}$ in gas phase as well as in condensed phase.

Figure 3 represents the lowest energy conformation obtained to **5a-d**. It is interesting to notice that the favored geometry for **5a** is slightly different from **5c** and quite different from **5b** and **5d** because of the dihedral angle $\phi_1$. For **5a**, the dihedral angle $\phi_1$ is related to the $O_1$-$C_5$-$C_6$-$O_2$ atoms, whereas for **5b-d** the dihedral angle $\phi_1$ is defined between $C_4$-$C_5$-$C_6$-$C_7$ carbon atoms. Moving up from 1 to 4 methylene units in the flexible spacer the preferred rotamers are those that contain all methylene units in *trans* conformation, except for **5a**. **5a** prefers a conformation where the two polar bonds $O_1$-$C_5$ and $C_6$-$O_2$ are disposable at angle of 173.3° to minimize the electrostatic repulsion in the *gauche* rotamer, where $\varphi_1$ angle is equal to 61.8°.

This conformational preference for **5a** can be explained by destabilizing interaction that occurs when the $O_1$-$C_5$ bond of the heterocyclic ring and $C_6$-$O_2$ of the ester group are in *gauche* position.

In the gauche arrangement (insert at the top of Figure 3), despite of $O_1$ is in opposite side of carbonyl oxygen $O_3$, $O_1$ and $O_2$ are closer than in *anti* conformation. To avoid this unfavorable electrostatic repulsion, **5a** showed more bent-shape form where $O_2$ and $O_1$ oxygen atoms have adopted *antiperiplanar* disposition. However when the size of flexible spacer increase by addition of methylene carbon atoms, this destabilization is no longer observed and now which is prevailing for flexible spacer is its preference for all *trans* conformations.

This preference can be explained by minimization of the destabilizing electrostatic interaction created by *gauche* conformations, thus avoiding the *syn*-pentane effect. A destabilizing *syn*-pentane interaction is created when a hydrocarbon chain is folded such that a $g^+$ dihedral angle is followed by one $g^-$ along the backbone.[32] This effect, primarily of steric origin, resulting in conformers substantially higher in energy and, for this reason, linear hydrocarbon chains in alkanes adopts conformations that are free of *syn*-pentane interactions.[33] This effect can be clearly seen in the even members **5b**, **5d**, and odd member **5c**.

Statistically, there are a lot of rotamers that contribute to the equilibrium of **5a-d** because of the great number of internal *degrees* of freedom on these molecules. For **5a**, considering the terminal alkyl chains all *trans*, there are two conformations with a small energy difference between them. One of them is more elongated (*gauche* conformer) and the other, the most stable, is more bent-shaped and less elongated (*anti* rotamer in Figure 3 – **5a**).

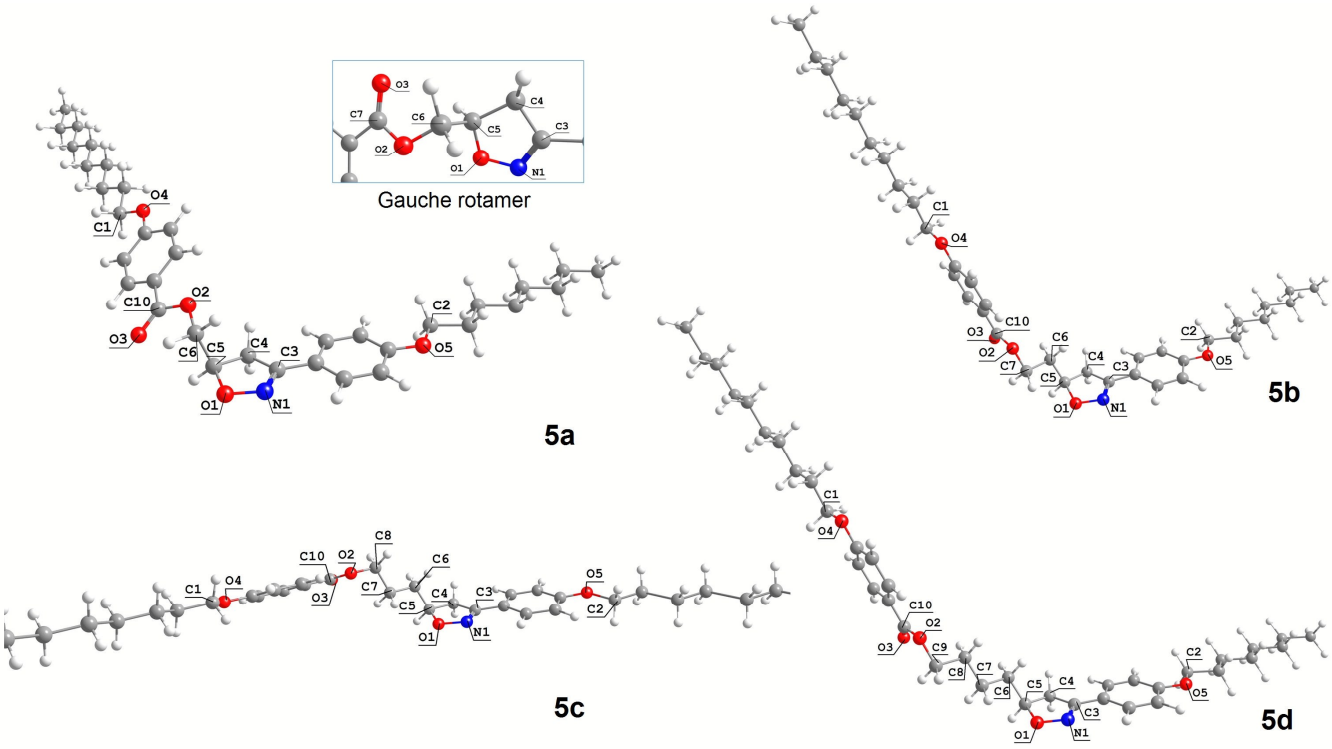


**Figure 3.** The most stable **5a-d** molecular structures calculated at B3LYP/6-311G(d,p) level, in gas phase. For **5a**, *gauche* rotamer is also inserted at the top of the view and *anti* rotamer (the most stable) is showed below. **5b-d** showed all *trans* conformation for flexible spacer.

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Statistically, there are a lot of rotamers that contribute to the equilibrium of **5a-d** because of the great number of internal *degrees* of freedom on these molecules. For **5a**, considering the terminal alkyl chains all *trans*, there are two conformations with a small energy difference between them. One of them is more elongated (*gauche* conformer) and the other, the most stable, is more bent-shaped and less elongated (*anti* rotamer in Figure 3 – **5a**). The energy barrier to convert the most stable rotamer obtained for **5a** into *gauche* rotamer is 0.67 kcal.mol$^{-1}$. Molecular length to *gauche* rotamer is 34.8 Å being about 6 Å bigger than *anti* rotamer. We can overlook the contribution of all conformers to the equilibrium if we restrict the conformers to a discrete number such as *anti* and *gauche* conformers.[34] In doing so the populations in the equilibrium are roughly estimate in favor to more bent-shape conformer (*anti*) than to the less bent-shape conformer (*gauche*).

The relative orientation of the two molecular planes depends on the conformation of flexible spacer (see Figure S33). The most stable conformer of **5a** presents two slightly collinear and twisted planes composed by aromatic rings, isoxazoline ring and terminal alkyl chains. The estimate angle between these two planes is about 32.5° from the side view (see SI). **5c** has similar planes which are shifted about 60° when compared to the planes of **5a**. These two planes are now separated by 21.5° from side view. Individually, each rotamer of **5a** has two independent planes which are organized in edge-to-edge manner. From the top view it is possible to see that planes are nearly flattened to the normal. For even members **5b** and **5d** these planes are bent. Rotamers of **5b** and **5d** are organized in face-to-face manner with an estimate angle between the planes of 98.5° and 102° for **5b** and **5d**, respectively. The top view of these planes shows that they are tilted to normal.

Table 2 shows the data for the most stable conformation of **5a-d**. The dipole moments, molecular length and some dihedral angles obtained to the *anti* conformation of **5a** in gas phase, water and cyclohexane are showed. For **5b-d** the data were collected only in gas phase. Both the gas phase and condensed phase calculations for **5a** pointed to same conformation as being the most stable conformer, but when solvent effects was into account the dipole moment increases with increasing of solvent dielectric constant.

The values of dihedral angles $\phi_2$, defined by $N_1$-$C_3$ and $O_5$-$C_2$, and $\phi_3$, defined by $O_2$-$C_{10}$-$O_4$-$C_1$, ensure that the alkyl chains and aromatic rings are in the same molecular plane on each side of the molecules. The aliphatic side chains have all trans conformation. The carbonyl oxygen, $O_3$, is always in opposite side to the $O_1$-$N_1$ polar bond of the isoxazoline ring, except to **5a**. In this structure, the carbonyl oxygen is on the same side of $O_1$-$N_1$ polar bond as a consequence of the *antiperiplanar* arrangement.

**Table 2.** Dipole moments (D), dihedral angles (degrees) and molecular length (Å) for **5a-d**. For **5a**, data in water and cyclohexane are also showed. Molecular lengths are calculated from carbon to carbon.

| Entry | μ (Debye) | Dihedral angle, $\phi_1$ | Dihedral angle, $\phi_2$[5] | Dihedral angle, $\phi_3$[6] | Molecular length (Å) |
|---|---|---|---|---|---|
| 5a | 7.7 | 173.3[3] | 179.4 | 176.5 | 28.96 |
| 5a[1] | 8.5 | 174.7[3] | 176.2 | 176.9 | 29.70 |
| 5a[2] | 9.8 | 177.0[3] | 175.1 | 176.8 | 29.80 |
| 5b | 5.4 | 175.6[4] | 179.8 | 178.0 | 33.25 |
| 5c | 3.0 | 176.7[4] | 0.660 | 0.86 | 36.93 |
| 5d | 5.0 | 176.9[4] | 176.5 | 178.6 | 37.45 |

[1]cyclohexane, [2]water; [3]dihedral angle between $O_1$-$C_5$-$C_6$-$O_2$ atoms; [4]dihedral angle between $C_4$-$C_5$-$C_6$-$C_7$ atoms; [5]dihedral angle $N_1$-$C_3$-$O_5$-$C_2$; [6]dihedral angle $O_2$-$C_{10}$-$O_4$-$C_1$.

The main feature of this conformational analysis is related to changes in the dihedral angle related to flexible spacer ($\phi_1$). The $\phi_2$ and $\phi_3$ dihedral angles are about 180.0° for **5a**, **5b**, and **5d** and about 0° for **5c**. Thus, **5a**, **5b**, and **5d** molecules display an *antiperiplanar* orientation of imine group (C=N) and $O_5$-$C_2$ bonds. The same *antiperiplanar* orientation is observed for acyl linkage ($OC_{10}$-$O_2$) and $O_4$-$C_1$ bonds. *Synperiplanar* orientation was observed for dihedral angles $\phi_2$ and $\phi_3$ only for **5c**. This is reflected in a lowering of dipole moment showed for this molecule.

Theoretical calculation is a powerful tool that helps us to understand the dependence of the thermal behavior on the length and the parity of the spacer observed for **5a-d** and **9a-d**, and even to **7a-d** which are definitely not a liquid crystal.[35] The even-odd effect in the melting point, and less visible to the enthalpy and entropy changes as the length of the spacers increase can be explained by the shape of the molecules considering the conformational issues of the flexible spacer.[36] Despite of the narrow energy barriers for the conformers observed in this study it is possible to assume that the conformers showed in Figure 3 are at least responsible for the observation of odd-even effects or partially responsible for behavior observed. We are assuming that, for example, compounds that have one and three carbon atoms in flexible spacer (odd members) are more anisotropic in their V-shape than the even members, and therefore their enthalpy and entropy values is higher than the even members.[37] Under this circumstances, the melting point to the odd members are

higher than even members for all compounds listed in Table 1 as a consequence of the better packing to the odd members. We are considering that molecular packing for odd members in an intermolecular V-fashion is face to face where the two molecular planes are nearly flattened to the normal. Even members may be packed one by one in V-fashion similar to chevron structure (Figure S44) considering that the planes are tilted to normal. So the odd members in this study can absorb more energy without causing disintegration of the crystals lattice until the melting point is reached.

The dependence of the transitional properties of LC **5a-d** and **9a-d** in relation to flexible spacer is better seen observing the melting point. The irregular behavior of mesophase makes the analysis more complex due to the enantiotropic or monotropic behavior observed for these LC (Table 1). The enthalpy values also show a similar effect being more pronounced for **5a-d** series. The entropy values follow the same tendency as observed for the compounds **5a-d** and **9a-d**. However, values of **5a-d** are higher due to transition occur from the ordered crystalline state to directly disordered liquid state. LC which enantiotropic mesophase such as **9a** or **9c** have an enhanced anisotropic-shape which allows a molecules to pack more efficiently in the mesophase resulting in higher transition temperatures and entropy changes.[2] It is possible to associate to these LC the synergy between the conformational distribution and the orientational order of the nematic phase.[33] The mesomorphic behavior found for **9a-d** in this work is due to the presence of the long aromatic moiety terminally bonded to the isoxazoline ring. However, in some cases such as **5a-d** or **7a-d** the molecular dimensions (length-to-breadth ratio) of the aromatic moiety are not sufficient to overcome the non-coplanarity of isoxazoline ring and the conformational issues of flexible spacer. In this situation no mesophase or unstable mesophase (i.e, monotropic behavior) appears.

**X-ray Experiments**

In Figure 4 we present the X-ray results obtained for compound **5a** by varying the temperature of the sample. The spectra were collected during cooling from the isotropic phase, where a broad halo is observed in the isotropic phase around $2\theta \approx 20°$, which according to Bragg's Law corresponds to a distance of about 4.5 Å. This distance is related to the short length correlations between neighboring molecules. It is worth emphasizing that the SmA and SmC phases are almost indistinguishable by X-ray experiments, where in both cases an intense peak appears in the low angle region as a result of the X-ray beam diffraction by the smectic layers. In this case, the assignment is possible with additional techniques as the polarizing optical microscopy.[38]

By applying Bragg's Law to the position of the first intense peak in the SmC phase at 80 °C it is possible to obtain an interlayer spacing of 28.3 Å, as well as, the second ordered peak at 14.6 Å. The ratio of $d_{001}/d_{002} \approx 2$ confirms the smectic character of the phase. The calculated molecular length (*L*) for compound **5a** in the lower energetic conformation between the external H atoms is 29.95 Å. Considering that the molecules adopt the most extended form of the aliphatic chains in the mesophase, the tilt angle ($\theta$) of molecules in the SmC phase can be determined with the expression $\theta = \cos^{-1}(d_{001}/L)$ = 19 degrees. Despite the fact that this value is relatively low, the same has been previously obtained for another SmC compound.[36] Inset of Figure 4 shows a schematic representation of the molecular packing according to the molecular optimized structure obtained by the theoretical analysis. Below the SmC – Cr transition temperature at 70 °C, additional peaks appear at the high angle region between 15 and 27 degrees, which are characteristic of the sample crystallization. However, at the low angle region an intense peak is still observed with an associated distance of 22.8 Å. It suggests that the smectic order is preserved, where the reduction of the interlayer distance compared to the one in the SmC phase can be associated to an increase of the tilt angle, to a reduction of the molecular length, or both.

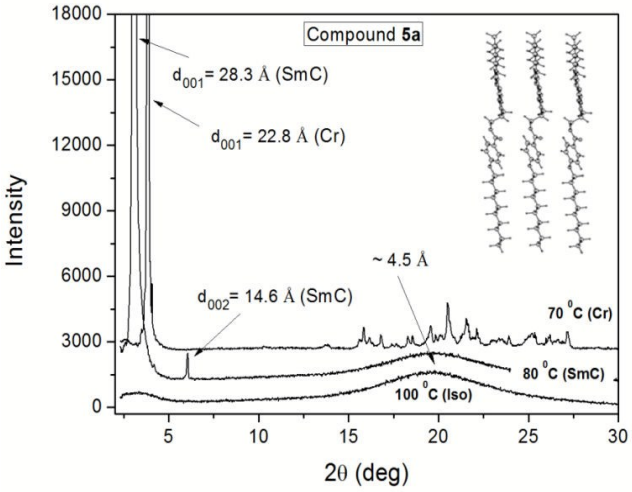


**Figure 4.** X-ray spectra of compound **5a** for different temperatures. Inset a schematic representation of the molecules in the layered structure.

For compound **5b** it was not possible to obtain a clear spectrum of the SmC phase, where the crystallization and the mesophase occur simultaneously.

## Conclusion

Two new series of non-symmetric liquid-crystalline dimers 3,5-disubstituted 4,5-dihydroisoxazole benzoates **5a-d** and **9a-d** have been synthesized. **5a** and **5b** displayed a monotropic SmC phase whereas **9a-d** displayed enantiotropic nematic phase for **9a** and **9c**. Monotropic behaviour was observed for **9b** and **9d**. The mesomorphic behavior observed over **9a-d** in this work is due to the presence of the naphthyl aromatic moiety laterally bonded to the isoxazoline ring. It was observed a dependence of the melting point on the length and the parity of the spacer for **5a-d** and **9a-d**, and even to **7a-d** which are not definitely a liquid crystal. Density functional theory calculations were performed to evaluate the conformational issues of the flexible spacers and how this question influences the mesomorphic behaviour of the dimers.

*Antiperiplanar* arrangement was found for all carbon atoms of the flexible spacer including the $C_4$ carbon atom of isoxazoline ring, except for **5a**. For **5a**, *antiperiplanar* arrangement was observed considering the oxygen atom $O_1$ of the isoxazoline ring. Otherwise, a less stable *gauche* rotamer for **5a** could be observed taking into account the alignment of carbon atom of flexible spacer with $C_4$ carbon atom of heterocyclic. Compounds that have one and three carbon atoms in flexible spacer (odd members) are more anisotropic in their V-shape than the even members. Melting point for both series **5a-d** and **9a-d** displayed a regular behaviour concerning the length and parity of the flexible spacer. Enthalpy and entropy values for **5a-d** esters accompanied the tendency observed of the melting point. However, for **9a-d** the behaviour was irregular.

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## Supplementary Information

Material Supplementary (Experimental procedure, $^{1}H$ and $^{13}C$ NMR spectrum and spectroscopic data final compounds, modeling pictures of the rotamers) is available free of charge at http://.....

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## Table of Contents - TOC

Liquid crystals behavior of the benzoates dimers **5a-d** and **9a-d** was dictated by conformational aspects of the flexible spacer.