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Liquid Crystal Control of Regio- and Diastereoselectivity in the Acid-Catalyzed Elimination of Alkyl Phosphates to Alkenes

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Abstract: The E1 reactions of *sec*- and *tert*-alkyl phosphates to isomeric olefins, as catalyzed by trifluoromethanesulfonic acid proceed smoothly with remarkably high regio- and diastereoselectivity in a smectic liquid crystalline phase medium, in contrast to isotropic reactions, which result in much lower selectivity. © 1997 Elsevier Science Ltd.

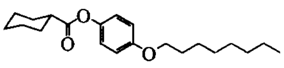
Over the past few years, a considerable amount of evidence has accumulated to indicate the potential value of liquid crystals as unique reaction media which are able to affect the chemical behavior of solute reactants by controlling their alignment.[1, 2] Over the last decade, the molecular ordering present in liquid crystalline phases has been shown to be sufficiently rigid to control thermochemical reactions conducted, even at elevated temperatures, particularly in carefully designed cases.[2] The ability of liquid crystalline solvents to regulate reactivity appears to depend on a number of factors including, shape, size, flexibility and polarizability of the reactant molecules and the type of mesophase of the medium.

In this paper we describe a remarkable example of stereochemical control exhibited by liquid crystalline solvents, in which a molecular shape of the product plays a major role in determining the course of the reaction.

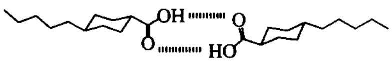
As a probe reaction we have explored the smooth acid-catalyzed elimination of *sec*- and *tert*-alkyl phosphates to give isomeric olefins[3] which likely proceeds *via* an E1 mechanism. The reaction involved the use of catalytic amounts of trifluoromethanesulfonic acid (TfOH) at 100 °C in a liquid crystal medium, as well as in isotropic solutions. Anisotropic solvents employed in this study involved the smectic diester, bis(4-octyloxyphenyl) *trans*-1,4-cyclohexanedicarboxylate (BOCD),[4] and the nematic carboxylic acid, *trans*-4-pentylcyclohexanecarboxylic acid (PCCA),[5] which exhibit mesomorphic ranges of 90 °-(Sm)-110 °-(N) -170 °C, and 53 °-(N)-105 °C, respectively. In addition to toluene, 4-octyloxyphenyl cyclohexanecarboxylate (OCC, mp 44 °C) and cyclohaxanecarboxylic acid (CCA, mp 30 °C), which are functionally similar to the

BOCD :

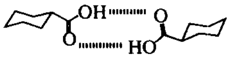
OCC :



PCCA :



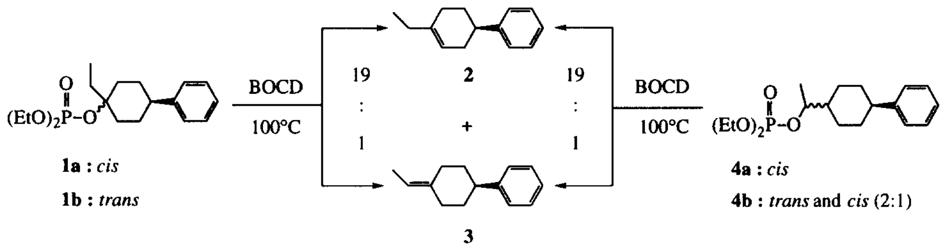
CCA :



mesogenic solvent molecules, were also used for comparison as isotropic solvents.

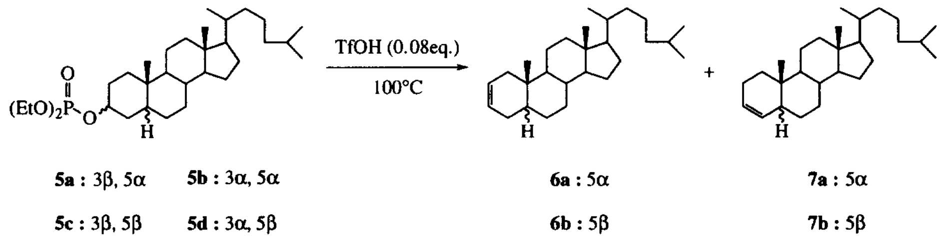
The BOCD type of smectic liquid crystal appears to have a strong affinity for rod-like 1,4-disubstituted cyclohexane derivatives, including steroidal skeletons as has been previously reported.[2] Thus, treatment of *cis*- and *trans*-4-phenylcyclohexyl phosphates (**1a** and **b**) with TfOH (0.25 equiv) in 30-fold equivalent weight amounts of a smectic solvent, BOCD, at 100 °C resulted in quantitative formation of the regioisomeric olefins **2** and **3** in a ratio of 19 : 1.[6] The concentration of the solutes was sufficiently low to maintain smectic reaction phases during the reaction period. In contrast, isotropic reactions performed in OCC and toluene gave the regioisomers with a lower selectivity of 10 : 1. The nematic solvent, PCCA, was not as effective as the BOCD solvent,[7] in enhancing the regioselectivity of olefin formation.

The elimination of *sec*-alkyl phosphates (**4a** and **b**) catalyzed by TfOH gave regioselectivity identical to that observed with **1a,b**, as might be expected, since the reaction probably proceeds *via* an E1 mechanism by carbocation rearrangement to give tertiary carbocations as a common intermediate. Thus, smectic (BOCD) and isotropic (OCC and toluene) reactions gave the ratios of 19 : 1 and 10 : 1, respectively.



Scheme 1

Another striking example of liquid crystal control was observed for the elimination of steroidal phosphates, such as 3-cholestanyl and 3-coprostanyl derivatives, which were treated with catalytic amounts of TfOH (0.08 equiv) in both anisotropic and isotropic solvents at 100 °C for 24 h. As seen in Table 1, the smectic reactions of 3β- and 3α-cholestanyl phosphates (**5a** and **b**) in a BOCD solvent proceeded equally well with excellent regioselectivity to give the 2- and 3-cholestenes (**6a** and **7a**) in a ratio of 32-34 : 1,[8] while the use of isotropic solvents resulted in a ratio of 5 : 1, and, hence, considerably poorer regioselectivity.



Scheme 2

Table 1. Acid-Catalyzed Elimination of Phosphates (**5**) to Alkenes (**6** and **7**) [a]

Compound	Solvent (phase) [b]	Temperature	**6a** : **7a** [c]
5a [**5b**]	BOCD(S)	100°C	32 : 1 [34 : 1]
5a [**5b**]	OCC(I)	100°C	5 : 1 [5 : 1]
5a [**5b**]	toluene(I)	100°C	6 : 1 [6 : 1]
5a [**5b**]	PCCA(N)	80°C	20 : 1 [20 : 1]
5a [**5b**]	CCA(N)	80°C	10 : 1 [10 : 1]
5c [**5d**]	BOCD(S)	100°C	4 : 1 [4 : 1] [d]
5c [**5d**]	OCC(I)	100°C	4 : 1 [4 : 1] [d]

a) The mixture of **5** and the solvent in a weight ratio of 1:30 was heated in the presence of TfOH (0.08 equiv) in an argon gas for 24 h. b) S: smectic. N: nematic. ; I: isotropic. c) Determined by ^{1}H NMR(500 MHz) and capillary GC analysis. d) Given in a ratio of **6 b** : **7 b**

A high level of regioselectivity was obtained only when the concentration was kept sufficiently low to maintain the liquid crystalline phases during the reaction period. The anisotropic rigidity of the solvent order was shown to be essential for the highly regioselective formation of olefins as seen in Fig. 1. A liquid crystalline solvent effect for the enhanced regioselectivity was also observed for the nematic reaction, performed at 80 °C, using PCCA solvent. On the other hand, such liquid crystal control was not a major factor in the elimination of 3-coprostanyl phosphates. Thus, the elimination reaction of 3β- and 3α-coprostanyl phosphates (**5c** and **d**) resulted in a 4 : 1 ratio of 2- to 3-coprostenes (**6b** and **7b**)[9] in either liquid crystalline or isotropic solvents.

The diastereoselective conversion of symmetrical phosphate (**8**) into (*E*)-1,3-diphenylpropene (**9a**) was achieved in smectic BOCD solvent. Treatment of **8** with an acid catalyst (TfOH) at 100 °C under the smectic medium gave the *E*-isomer (**9a**) with excellent diastereoselectivity above 90%de, while the isotropic reaction (OCC solvent) resulted in much lower selectivity (Scheme 3).

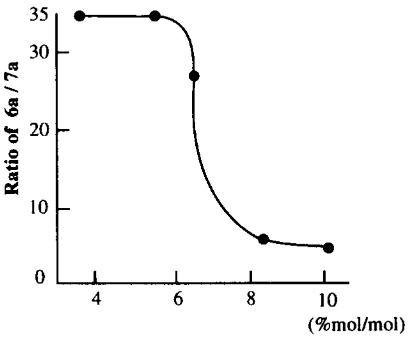
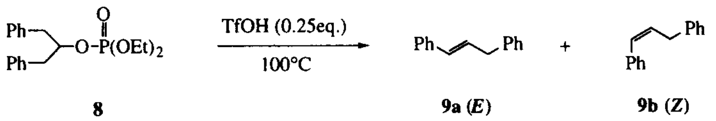


Figure 1. A plot of isomer ratio as a function function of concentrations of the solute for acid-catalyzed elimination of **5a** to **6a** and **7a** in BOCD at 100°C.



	9a (*E*)		**9b** (*Z*)
BOCD (S)	20	:	1
OCC (toluene) (I)	4 (4)	:	1 (1)

Scheme 3

For the isomeric olefins explored in this study, no isomerization was observed on prolonged treatment under the reaction conditions employed. The high regioselectivity observed in smectic reaction media can be rationalized by postulating that the transition states were firmly accommodated into the liquid crystalline solvent matrix, thus leading to the preferential formation of olefinic isomers from the common carbocation intermediates.

In conclusion, the results presented here demonstrate the high potential of liquid crystals as reaction media to regulate various aspects of reactivity. It should again be noted that such liquid crystal control is heavily dependent on the structural features of the guest molecules.

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6. Compound **2** : δ 5.48 (m, 1H). Compound **3** : δ 5.20-5.24 (m, 1H).
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7. Acidic treatment of **1** and **4** in nematic PCCA solvent resulted in a 13 : 1 ratio of **2** and **3**, while the isotropic reactions in CCA gave the ratio of 9-10 : 1 under the identical conditions.
8. Compound **6a** : δ 5.59 (m, 2H). Compound **7a** : δ 5.27-5.29 (m, 2H).
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9. Compound **6b** : δ 5.49 (m, 2H). Compound **7b** : δ 5.31-5.36 (m, 1H), δ 5.62-5.69 (m, 1H).
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