Organic Reactions in Liquid-Crystalline Solvents. Regiochemical Control of Bimolecular Pericyclic Reactions by Cholesteric and Smectic Liquid-Crystalline Solvents

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Abstract: The addition reactions of N-phenyl, N-para-biphenyl, and N-para,para'-terphenyl-maleimide with 7-dehydrocholesteryl acetate have been carried out in the isotropic and cholesteric liquid crystalline phases of a series of steroidal mesogens, and in the isotropic, smectic A, and smectic B phases of 4,4'-dialkylbiphenyl mesogens at temperatures between 180 and 240 °C. In isotropic solvents, mixtures of four adducts are obtained, in relative yields that are essentially independent of the maleimide substituent. The three major products (two ene-adducts and one Diels-Alder adduct) are formed via transition states in which the long molecular axes of the reactants are oriented perpendicular to one another, while the fourth (minor) product is an ene-adduct formed via a transition state with a parallel relative orientation of the reactants' long molecular axes. The relative yield of the latter product is enhanced when the reaction is carried out in cholesteric or smectic liquid crystalline solvents, to an extent which correlates with both the degree of order possessed by the liquid crystal and the molecular length of the N-arylmaleimide employed. For example, this adduct is the major product of reaction of N-para,para'-terphenylmaleimide with **1** in the cholesteric phase of cholesteryl para-chlorobenzoate at 200 °C. Studies of the temperature dependence of the product distributions afford estimates of the difference in enthalpy and entropy between parallel and perpendicular transition states in the cholesteric phase. The effect of the smectic B phase on the activation parameters appears to be smaller than that of the cholesteric phase; it is suggested that this is due to poor solubility of the reactants in the smectic phase, which leads to complex variations in reactant solubilization and reactivity as a function of temperature. The smectic A phase of this mesogen exerts much greater control on reactivity than the cholesteric phases at 240 °C.

Introduction

The use of thermotropic liquid crystals to alter the course and rates of uni- and bimolecular thermal and photochemical reactions has been a subject of considerable interest over the last 20 years and has been recently reviewed.[3-5] Nematic and cholesteric liquid crystals are ordered fluids in which the constituent molecules are oriented parallel to one another (on average) on a microscopic level.[6] Cholesterics can be viewed as optically active versions of simple nematics; as one proceeds through the bulk of the sample, there is a macroscopic twist in molecular alignment which results in a helical structure. Smectic phases are also characterized by parallel ordering of the constituent molecules, but there is further arrangement into layers whose planes are perpendicular (or at some angle close to perpendicular) with respect to the molecular axes. Smectic phases are classified according to the degree and type of molecular ordering within the layers and according to the angle subtended by the molecular axes and the layer planes. In smectic "B" (Sm_B) phases, the constituent molecules are arranged in hexagonally close-packed layers whose planes are perpendicular to the molecular axes. Smectic "A" (Sm_A) phases are also thought to be layered structures, but there is little or no positional regularity of the constituent molecules within the layers.[6]

One way in which these media are thought to alter chemical reactivity is by imparting constraints on reaction transition states due to size/shape considerations; liquid crystals favor reactions whose transition states are structurally most compatible with the ordered solvent matrix.[5] This follows quite logically from consideration of various known properties of solute/liquid-crystal systems.[6] The ability of liquid crystals to alter solute reactivity in such a fashion has been most effectively demonstrated with unimolecular photochemical reactions whose product distributions (or rates) depend on conformational factors.[7-11]

Several studies of the potential effects of liquid crystals on bimolecular reactions have also been reported. Photochemical studies have concentrated on [2 + 2] cycloaddition reactions[12-15] and on pyrene excimer/exciplex formation.[4b] In these cases, liquid crystals are thought to alter the efficiency and stereochemistry of the reaction as a result of size/shape considerations as well as reactant orientational effects. Thermal bimolecular reactions which have been studied in liquid crystals include free-radical dimerization[16] and hydrogen abstraction reactions,[17] sulfonate ester rearrangements,[18] and Diels-Alder[19] and ene addition reactions.[20]

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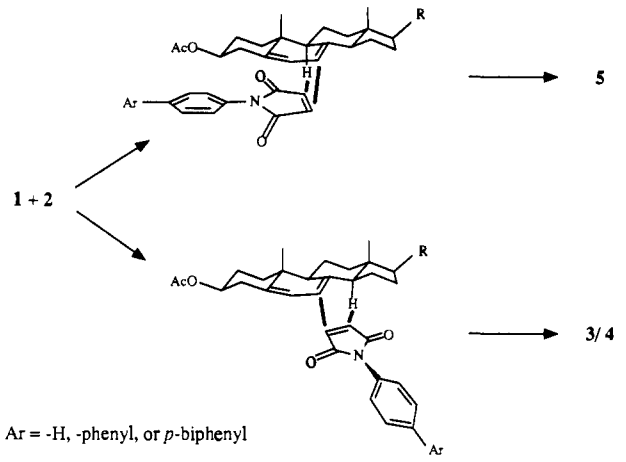
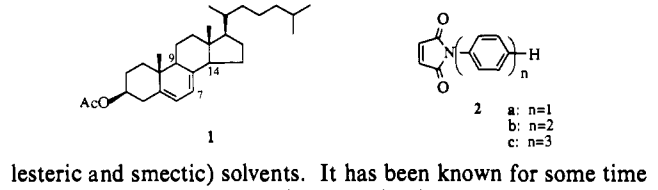
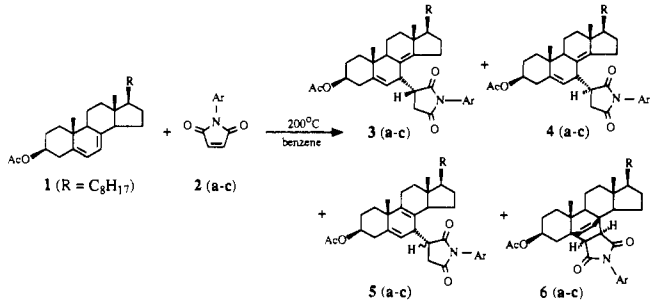
Scheme I. Reactant Orientation in the Transition States for Formation of Ene Adducts 3–5



As part of our continuing studies of the effects of thermotropic liquid crystals on the thermal and photochemical reactivity of dissolved solutes, we have carried out a study of the thermal addition reactions of 7-dehydrocholesteryl acetate (**1**) with a series of *N*-arylmaleimides (**2**) in isotropic and liquid-crystalline (cholesteric and smectic) solvents. It has been known for some time that steroidal 5,7-dienes undergo predominant ene addition with electron-deficient olefins in isotropic solvents.[21] With cyclic enophiles such as **2**[20,22] or maleic anhydride,[23] three stereoisomeric ene adducts are formed, along with minor amounts of a Diels–Alder adduct. The products obtained from reaction of **1** and **2** in benzene solution are shown in eq 1.[20,22] Formation of the ene





(1)

adducts results from addition of the enophile to C-7 of the steroid, with concomitant abstraction of the proton at either C-9 (leading to product **5** in eq 1) or C-14 (leading to products **3** and **4** in eq 1) and corresponding double-bond shift. In isotropic solvents such as benzene, **3** and **4** are the major products of reaction of **1** and **2**.

The transition states for concerted formation of the C-9 and C-14 adducts (**5** and **3** + **4**, respectively) differ dramatically in size and shape owing to differences in the required relative orientation of the two reactants (see Scheme I). Formation of the C-9 adduct (**5**) requires a parallel reactant orientation in the transition state, while formation of the C-14 adducts (**3** and **4**) requires a perpendicular (endo or exo) reactant orientation.

In a preliminary note, we have reported that the yield of the "parallel" ene adduct (**5b**) from reaction of **1** and **2b** is enhanced at the expense of those of the "perpendicular" ene (**3b**, **4b**) and Diels–Alder adducts (**6b**) (compared to the relative product yields in model isotropic solvents) when the reaction is carried out in cholesteric or smectic B liquid-crystalline solvents.[20] We ascribed this effect to an ability of the ordered solvent to discriminate between parallel and perpendicular transition states on the basis of their size/shape compatibilities with the ordered solvent matrix. As might be expected from this model, the magnitude of the effect observed is larger in the more highly ordered smectic liquid crystal than in the relatively weakly ordered cholesteric phases, although the difference between the two phase types is not particularly large.

In this paper, we report the results of further studies of the effects of cholesteric and smectic liquid crystals on this reaction. These additional studies have been designed with several goals in mind. The first was to probe the relationship between the effectiveness with which liquid crystals can control reactions of this type and the molecular length of the reactants; one would expect that as the length of one or both of the reactants is increased, so too would the difference between the bulk shapes of the parallel and perpendicular transitions states and, hence, the ability of the liquid crystal to discriminate between them. Thus, we have extended our study to include the reactions of **1** with *N*-phenylmaleimide (**2a**) and *N*-(*p*,*p*′-terphenyl)maleimide (**2c**) in order to examine enophiles which are shorter and longer (respectively) than *N*-(*p*-biphenyl)maleimide (**2b**), the subject of our initial communication.[20]

We have also studied the variation in the product distribution obtained from reactions of **1** and **2c** as a function of temperature in cholesteric and smectic B liquid crystals and in related model isotropic solvents, in the hope of defining the nature of the medium effect more quantitatively and to better understand the relatively small difference between the effects observed (for **1** and **2b**) in cholesteric and smectic B phases. The results of these studies are reported below.

Table I. Transition Temperatures of Neat and Solute-Doped Cholesteric Liquid Crystals[a]

mixture	T_{K-Ch}[b]	T_{Ch-I}[b]
CnB	135.5–136.5	156.6–157.0
CnB + 1.76% (**1** + **2c**)	131.5–135.0	152.0–155.0
CnT	172.3–173.0	229.0–230.0
CnT + 1.76% (**1** + **2c**)	168.0–172.3	226.2–227.5
ChCB	166.0–168.0	250.0–253.0
ChCB + 1.76% (**1** + **2c**)	164.5–168.0	241.0–249.5

[a] Measured by thermal microscopy; in °C. [b] K = solid; Ch = cholesteric; I = isotropic.

Results

The reactions of **1** and **2a–c** in benzene solution and the isolation and identification of the corresponding ene (**3–5**) and Diels–Alder (**6**) adducts have been described in detail elsewhere.[22]

The mesogenic compounds employed as reaction solvents have the general structures shown below. The cholesteryl and cholestanyl esters were synthesized by standard procedures and purified by repeated recrystallization, while the biphenyl derivatives were obtained commercially. Table I lists phase transition temperatures recorded for CnB,[24] CnT,[24] and ChCB[25] and for mixtures of the three mesogens with equimolar amounts of **1** and **2c** (1.76 wt % total). Transition temperatures were also recorded for 1.5 and 1.6 wt % mixtures of **1** + **2a** and **1** + **2b**, respectively, in each of these mesogens. They did not differ significantly from those

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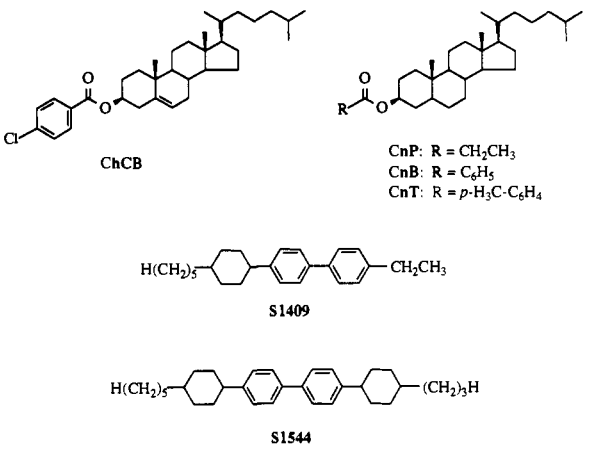

of the **1**/**2c** mixtures. CnP does not exhibit a cholesteric liquid-crystalline phase.

Pure S1544 exhibits the following phase transition temperatures: K-(54°)-Sm_B-(232°)-Sm_A-(251°)-N-(312°)-I.[26] Thermal microscopic analysis of mixtures of **1** and **2** (1.5–1.76 wt %) with S1544 proved to be difficult owing to the polymorphic nature of this smectogen but showed some evidence of biphasic behavior within the Sm_B phase temperature range above ca. 200 °C. Because of these difficulties, a 5 wt % sample of (equimolar) **1** and **2c** was examined by thermal microscopy. Cooling the sample from ca. 260 °C results in the N-Sm_A transition at 245.0–247.0 °C. The Sm_A phase appears to be homogeneous to 226 °C, below which the transition to the Sm_B phase gradually commences, as evidenced by the appearance of small monodomains of considerably greater rigidity than that of the bulk Sm_A phase. Tapping of the sample slide as the temperature is lowered further reveals that the Sm_A phase persists (in decreasing proportion with temperature) to as low as 180 °C, below which the sample is uniformly rigid and shows the classic mosaic texture of the Sm_B phase.[27]

Equimolar samples of **1** and **2a–c** (1.5–1.76 wt % total reactants) in each of the mesogenic solvents were sealed in Pyrex tubes and heated in a constant temperature bath at 200 °C for 2–4 h (6–12 h for the reaction of **1** and **2c** in S1544), to a total conversion of 40–70%. The reaction mixtures were analyzed by high-performance liquid chromatography. In each case, a mixture of five adducts (the same as those obtained from thermolyses in benzene solution) is obtained, four of which have been isolated and identified.[22] Isolated samples of the adducts from reaction of **1** and **2b** (**3b–6b**) were shown to be stable to prolonged heating at 200 °C (>10 h). Table II lists the product yields from reaction of **1** and **2a–c** in the various solvents. Adducts **4** and **6** from the reaction of **1** with **2b** and **2c** could not be isolated under the HPLC conditions employed for our analyses[22] and were thus analyzed together. The product yields reported in Table II are the averages of three runs, each analyzed in triplicate.

The reaction of **1** and **2** was carried out at six temperatures between 180 and 240 °C in the isotropic phases of CnB and S1409, the cholesteric phase of ChCB, and the Sm_A and Sm_B phases of S1544, with thermolysis times adjusted at each temperature to correspond to 30–50% conversion of reactants. No new products are formed at any temperature in any of the four solvents. The product ratios obtained from these experiments are collected in Table III.

Discussion

The product yields from reaction of **1** with *N*-phenylmaleimide (**2a**) in the cholesteric phases are only slightly different from those obtained in the model isotropic phases. A slight increase in the yield of adduct **5a**—that formed via the parallel transition state depicted in Scheme I—is perceptible in the cholesteric solvent. The increase is more dramatic in the smectic phase of S1544, in this case using isotropic S1409 for comparison. Substantial increases in the yield of adduct **5** from both **2b** and **2c** are observed in the liquid-crystalline phases. The behavior of the *N*-terphenyl derivative is most striking; in this case, adduct **5c** (the minor product in isotropic solvents) is the major product of reaction in the cholesteric and smectic B liquid crystals. The substantially greater yield of **5c** in liquid-crystalline solvents compared to isotropics make it practical to employ cholesteric solvents for the synthesis of this adduct on a semipreparative (200–300 mg) scale.[22]

Figure 1 shows a plot of the ratio of the yield of (parallel) adduct **5** to (perpendicular) adduct **3** as a function of aryl chain length in the *N*-arylmaleimides **2a–c**, for reactions carried out in the three liquid-crystalline phases and two of the model isotropic solvents. The plot illustrates several characteristics of the reaction

Table II. Product Yields from Thermolysis of Mixtures of **1** and **2a–c** in Isotropic and Liquid-Crystalline Solvents at 200 °C[a]

solvent	**1** + **2a**[b] (3:4:5:5)	**1** + **2b**[c] (3:[4+6]:5)	**1** + **2c**[d] (3:[4+6]:5)
benzene[e]	36:25:19:13	32:48:13	32:47:15
CnB (I)	33:23:21:16	31:43:17	27:45:18
CnP (I)	34:24:19:16	32:42:16	30:45:17
CnT (Ch)	33:22:18:20	27:32:29	24:26:36
ChCB (Ch)	34:20:18:20	25:29:33	21:23:40
S1409 (I)	34:24:21:15	31:44:14	30:44:18
S1544 (Sm_B)	31:17:17:28	23:30:38	13:26:49

[a] Product yields were determined by HPLC analysis and are the average of three runs analyzed in triplicate. The standard deviation in the yields is ±0.3%. [b] The mixtures contained one unidentified minor product, formed in yields of 6–7% in the isotropic phases, 8.7 ± 0.2% in the cholesteric phases, and 7.3% in S1544. All samples were 1.5 wt % total reactants. [c] The mixtures contained one unidentified minor product, which was formed in yields of 7–10% in the isotropic phases, 12–13% in the cholesteric phases, and 9% in S1544. All samples were 1.6 wt % total reactants. [d] The mixtures contained one unidentified minor product, which was formed in yields of 7–10% in the isotropic phases, 13–16% in the cholesteric phases, and 11% in S1544. All samples were 1.76 wt % total reactants.

Table III. Product Yields from Thermolysis of **1** and **2c** in CnB (isot), ChCB (chol), S1409 (isot), and S1544 (sm) as a Function of Temperature[a]

	3:[4+6]:5:?[b]			
T, °C	CnB (isot)	ChCB (chol)	S1409 (isot)	S1544 (sm)
180	27:44:19:9	19:20:47:14	29:45:19:8	12:28:47:13
200	27:45:18:10	21:23:40:16	30:44:18:8	13:26:49:11
210	29:41:20:9	21:26:40:14	30:42:19:9	15:23:51:12
220	29:40:20:10	23:24:37:15	31:39:20:9	15:17:51:17
230	32:35:22:12	25:24:36:15	32:37:20:11	16:12:56:16
240	32:34:22:12	26:32:30:13	33:37:20:11	17:12:54:17

[a] Product yields were determined by HPLC analysis and are the average of three runs analyzed in triplicate. The standard deviation in the yields is ±0.3%. [b] "?" refers to the unidentified minor product of the reaction.

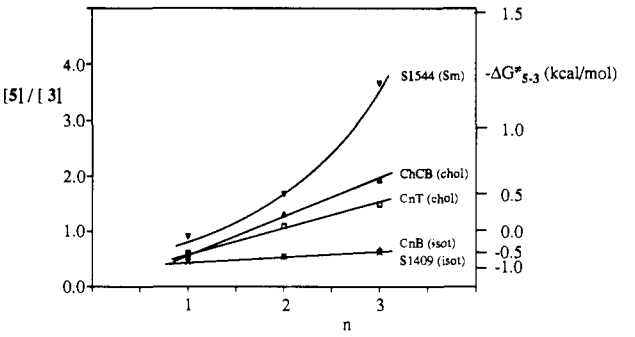

Figure 1. Plot of the ratio of the yield of adduct **5** to that of adduct **3** vs *n*, the number of phenyl groups in *N*-arylmaleimide **2**, from the reaction of **1** and **2a–c** in mesogenic solvents at 200 °C (data calculated from that given in Table II).

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in the various solvents. Firstly, there is very little change in the relative yields of **5** and **3** with *N*-aryl substituent in isotropic solvents (including benzene,[22] data for which are not included in Figure 1). Secondly, the increase in the relative yield of adduct **5** that occurs in liquid-crystalline solvents compared to isotropics is proportional to the molecular length of the reactants. This demonstrates that the ability of a liquid crystal to discriminate between product transition states on the basis of differences in their size and shape depends on the magnitude of this difference. Thirdly, the magnitude of the effect which is observed depends on the degree of order possessed by the liquid crystal. This is particularly evident when the data for the (highly ordered) Sm_B phase of S1544 are compared to those obtained in the (considerably less ordered) cholesteric phases. It is interesting that an analogous (though much smaller) trend is observed for the two cholesteric phases investigated. ChCB and CnT were specifically chosen for study because of their different cholesteric temperature ranges; the former is cholesteric from 166 to 250 °C, while the latter is cholesteric from 172 to 229 °C. At the reaction temperature (200 °C), CnT is thus closer to its Ch–I transition temprature than ChCB is, there is less order present in the liquid crystal,[6] and it is correspondingly less effective in discriminating between parallel and perpendicular products on the basis of size/shape differences. Similar effects have been observed with conformation-dependent unimolecular reactions in smectic phases.[11] It should be noted, however, that the validity of this explanation assumes that there are no intrinsic differences in the effectiveness with which the reactants are solubilized in the two steroids. Given the fact that the two steroidal mesogens are somewhat different in structure, this assumption is difficult to validate.

The product ratio ([**5**]/[**3**]) is a sensitive function of the difference in the free energies of the transition states for formation of the two products from the reaction of **1** and **2** (eq 2).[28] Thus,

$$[\mathbf{5}]/[\mathbf{3}] = \exp(-\{G^{\ddagger}_{5} - G^{\ddagger}_{3}\}/RT) = \exp(-\Delta G^{\ddagger}_{5-3}/RT) \qquad (2)$$

the variation in this product ratio with reactant length (for a given liquid crystal) and liquid-crystalline order (for a given *N*-arylmaleimide) provides a direct measure of the effect of these variables on the relative free energies of the two transition states. In the case of the two cholesteric phases, $\Delta G^{\ddagger}_{5-3}$ (as estimated from the product ratios using eq 3) increases by 0.9–1.1 kcal/mol as the enophile molecular length increases throughout the series **2a–c** (see Figure 1). This should be compared to the parallel variation of ca. 0.3 kcal/mol in $\Delta G^{\ddagger}_{5-3}$ throughout the series of enophiles for the model isotropic phases (CnB and CnP). The variation is slightly larger for ChCB than for CnT, as mentioned previously. It is interesting that the corresponding span in $\Delta G^{\ddagger}_{5-3}$ is only slightly higher in the Sm-B phase of S1544 (≈1.3 kcal/mol) than in the cholesteric phases, in spite of the considerably higher degree of order inherent in this type of liquid crystal. The reasons for this behavior will be discussed in more detail later.

For the reaction of **1** with **2c** in the isotropic solvents and in cholesteric ChCB, increasing the reaction temperature causes the relative product yields to shift toward equal values, as would be expected for a system of this type in which all the products are formed by bimolecular, pericyclic mechanisms in homogeneous solution.

Figure 2 shows a semilogarithmic plot of the ratio of yields of adducts **5c** and **3c** versus inverse temperature from data collected in cholesteric ChCB and isotropic CnB. The slopes and intercepts of the plots yield $\Delta H^{\ddagger}_{5-3}$ and $\Delta S^{\ddagger}_{5-3}$, the differences in enthalpy and entropy of the transition states leading to parallel and perpendicular ene adducts in the cholesteric and model isotropic solvents (eq 3). Least-squares analysis of these data gives $\Delta H^{\ddagger}_{5-3}$

$$\ln\{[\mathbf{5}]/[\mathbf{3}]\} = -\Delta H^{\ddagger}_{5-3}/RT + \Delta S^{\ddagger}_{5-3}/R \qquad (3)$$

= 0.0 ± 0.4 kcal/mol and $\Delta S^{\ddagger}_{5-3}$ = −0.8 ± 0.8 eu for isotropic

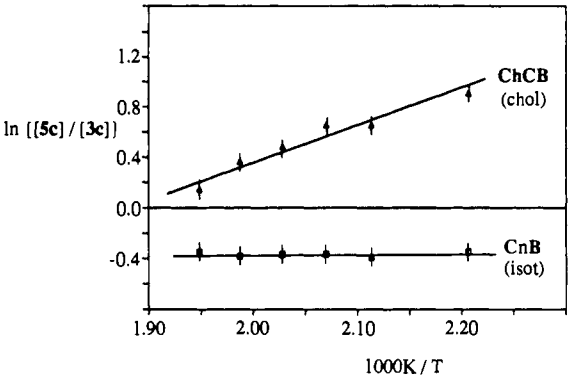

Figure 2. Semilogarithmic plot of the ratio of the yield of adduct **5c** to that of adduct **3c** vs inverse temperature, from the reaction of **1** and **2c** in isotropic cholestanyl benzoate (CnB; Δ) and the cholesteric phase of cholesteryl 4-chlorobenzoate (ChB; □) between 180 and 240 °C. The error bars represent 95% confidence limits of the data.

CnB and $\Delta H^{\ddagger}_{5-3}$ = −5.0 ± 1.0 kcal/mol and $\Delta S^{\ddagger}_{5-3}$ = 9 ± 2 eu for the cholesteric phase of ChCB. Phase transition temperatures of a mixture of **1** and **2c** in ChCB after thermolysis to ca. 50% conversion do not differ significantly from those of the mixture prior to thermolysis; the bulk morphology of the mixture is thus reasonably constant and well-defined throughout the complete reaction period, even at 240 °C. This suggests that the observed differences in transition-state enthalpy and entropy can be attributed solely to effects of the cholesteric medium on the reaction and are not artifacts due to biphasic solubilization of the reactants at higher temperatures within the cholesteric range.

We interpret the values $\Delta H^{\ddagger}_{5-3}$ and $\Delta S^{\ddagger}_{5-3}$ as the difference in the solvation enthalpy and entropy of the reactive complexes leading to parallel and perpendicular ene adducts in the cholesteric medium; the cholesteric phase stabilizes the parallel transition state by 5 ± 1 kcal/mol relative to the perpendicular one. Presumably, the positive entropy difference (which favors the perpendicular adduct by 9 ± 2 eu) is due to the relatively greater degree of disruption to the solvent matrix which accompanies formation of the perpendicular adduct compared to the parallel one.

The extent to which the cholesteric medium stabilizes the transition state leading to **5** relative to that for **3** may seem surprisingly large, considering that the cholesteric–isotropic transition enthalpy is typically on the order of only 0.1–0.3 kcal/mol.[6] However, as Sergeev and co-workers have pointed out,[16b] the correct parameter to compare this value to is the solute/mesogen interaction energy for the liquid-crystalline phase. While this is difficult to determine, it is instructive to consider the energy of interaction of the solvent molecules with each other in the liquid-crystalline phase, as an upper limit for the interaction energy obtainable in a solute/mesogen system. This has been calculated to be on the order of 2–3 kcal/mol for nematic liquid crystals[17,29] and would presumably be somewhat larger for cholesteric phases. The value of $\Delta H^{\ddagger}_{5-3}$ observed for the reaction of **1** with **2c** in cholesteric ChCB is clearly in line with what might be expected on the basis of these qualitative considerations.

The variation in the product distribution from reaction of **1** and **2c** in S1544 with temperature (Table III and Figure 3) exhibits some unusual features. Firstly, the variations in relative adduct yields with temperature appear to be contrathermodynamic; the yield of the major product (**5c**) *increases* with increasing temperature, while the yield of the minor products **4c** and/or **6c** (these were analyzed together) *decreases*. Secondly, the product distribution obtained from reaction at 240 °C, when the sample is in the Sm_A phase, is very similar to that obtained at lower temperatures where the bulk of the sample is in the Sm_B phase. Sm_A phases possess nematic-like local order and would thus be expected to exert much weaker control on reactivity than Sm_B phases, a

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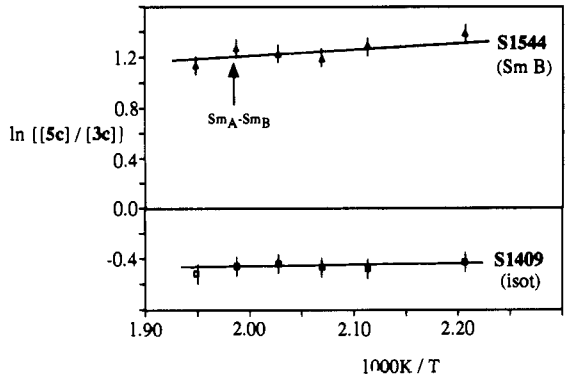

Figure 3. Semilogarithmic plot of the ratio of the yield of adduct **5c** to that of adduct **3c** vs inverse temperature, from the reaction of **1** and **2c** in isotropic S1409 (□) and the smectic phase of S1544 (△) between 180 and 240 °C. The arrow designates the Sm_A–Sm_B phase transition temperture of pure S1544 (232 °C). The error bars represent 95% confidence limits of the data.

priori. Finally, the variation in the [**5**]/[**3**] ratio with temperature in S1544 is remarkably slight, in spite of the significantly more pronounced effect of this mesophase on the product distribution at 200 °C compared to that of cholesteric ChCB (vide supra). Figure 3 shows the plots of ln {[**5**]/[**3**]} vs inverse temperature for the reaction of **1** and **2c** in S1544 and S1409. The Sm_A–Sm_B transition temperature for pure S1544 is labeled in the figure.

We believe that these unusual characteristics are at least partially due to biphasic solubilization of the reactants in the smectogen throughout the 180–230 °C temperature range, as indicated by the thermal microscopy experiments described earlier. If this is the case, then the observed product ratios are average values of those due to reaction of the solutes in the Sm_B phase and in the coexisting, more weakly ordered Sm_A phase, weighted according to the distribution of the reactants between and the relative rate constants for reaction in the two coexisting phases. Unraveling the contributions of the two individual phase types to the overall, observed product ratios is an exceedingly complex task since the distribution and concentrations of the reactants in the two phases is temperature-dependent. In principle, rather simple variations in the physical nature of the reactant/mesogen system with temperature (which follow from the temperature/composition phase diagram[30] can result in complex variations in product distribution owing to a number of interrelated factors. At temperatures close to 230 °C, the reactants will be solubilized predominantly in the Sm_A phase, at concentrations which are close to the bulk values. At temperatures close to 180 °C, the reactants will be solubilized to a somewhat greater extent in the Sm_B phase, which comprises the bulk of the sample. The concentrations of reactants in the Sm_A portion of the mixture under these conditions is likely to be extremely high, however; this should have the effects of increasing the rate of reaction in this portion of the mixture, as well as leading to lesser discrimination between product types owing to a lower degree of order in the phase as a result of the high concentration of solutes. One must also take into account the fact that the system itself changes with time as reactants are replaced with products. It is likely that the reaction is faster in the Sm_A component than in the more solidlike Sm_B component where diffusion of the reactants is considerably slower (we have observed that reaction of **1** and **2** at 200 °C is markedly slower in S1544 than in the other solvents studied; vide supra). Thus, at short reaction times, the observed product distribution may in fact reflect that arising from reaction in the Sm_A phase predominantly.

The data obtained for S1544 at 240 °C define the effect of the Sm_A phase on the reaction of **1** and **2c** and should be compared with the data for ChCB and S1409 at the same temperature. It is clear that this phase exerts considerably greater control over the reaction than the cholesteric phase does at the same temperature. Unfortunately, experimental limitations prevent detailed investigation of the temperature dependence of the reaction in the Sm_A phase. Similarly, analytical problems prevent us from obtaining an accurate indication of the product ratios characteristic of homogeneous solubilization in the Sm_B phase, since this requires the use of samples of much lower bulk concentrations of reactants.

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Summary and Conclusions

Thermal addition of 7-dehydrocholesteryl acetate (**1**) and a series of *N*-arylmaleimides (**2a–c**) yields a mixture of ene and Diels–Alder adducts formed by transition states in which the rodlike reactants must align themselves either parallel or perpendicular to one another. Liquid crystals enhance the yield of the adduct formed by the parallel transition state at the expense of the others, to an extent which correlates with the molecular length of the reactants and with the degree of order possessed by the mesophase. Cholesteric liquid crystals, in spite of the fact that they are relatively weakly ordered, are surprisingly effective at controlling the reaction with *N*-biphenyl- and *N*-terphenylmaleimide (**2b** and **2c**, respectively). Part of the reason for this is the fact that the structure of **1** is similar to that of the mesogen, which allows it to be solubilized relatively unobtrusively in the liquid-crystalline lattice. The temperature dependence of the product distribution from the reaction of **1** and **2c** affords estimates of the differences in the enthalpy and entropy of solvation of the parallel and perpendicular transition states in the cholesteric phase.

Interpretation of the effect of the smectic B phase of S1544 on the reaction is complicated due to low solubilities of the reactants in the mesophase, although at all temperatures studied, the enhancement in the yield of the parallel adduct is greater in the smectogen than in the cholesteric phase. The smectic A phase of S1544 is dramatically more effective in controlling the reaction of **1** and **2c** than cholesteric phases at the same temperature.

Experimental Section

Melting points and transition temperatures were determined using a Mettler FP82 hot stage (controlled by a Mettler FP80 central processor) mounted on an Olympus BH-2 microscope and are corrected.

Analytical high-performance liquid chromatographic analyses employed a Gilson Isocratic HPLC system consisting of a Model 302 pump and 5-mL head, a Model 802B manometric module, Holochrome variable-wavelength detector, a Rheodyne Model 7125 loop injector, and a Merck Hibar (25- × 0.46-cm) Si60 (10-μm) column. A detector wavelength of 235 nm was used for analysis of product mixtures from reactions of **1** and **2a**. Analyses of those from reaction of **1** with **2b** and **2c** employed a detector wavelength of 280 nm. The detector was interfaced with a Unitron microcomputer (Apple II+ clone) through an Adalab data acquisition/control card (Interactive Microware, Inc.). The 0–10-mV signal was amplified to 0–1 V using an Adaamp analog amplifier (Interactive Microware, Inc.). Chromatogram acquisition and storage was performed using Chromatochart (Interactive Microware, Inc.).

Thermolyses employed a constant-temperature bath consisting of an insulated 4-L stainless steel beaker containing silicon oil (Dow-Corning 710). The oil was heated by a heating coil encased in a quartz tube, which was regulated by a Jumo-MS DBP mercury thermoregulator and Fisher Model 32 transistor relay. Temperatures were measured using a Cole-Parmer Model 8110-10 Type K thermocouple thermometer and did not vary by more than ±0.2 °C during the course of a run. Temperatures are considered accurate to ±1.0 °C.

HPLC solvents (acetonitrile—Caledon HPLC), dichloromethane (Caledon HPLC), ethyl acetate (BDH Reagent), and hexane (Caledon HPLC) were used as received from the suppliers. The mesogenic solvents S1409 and S1544 were used as received from E. Merck & Co. *N*-Phenylmaleimide (Sigma) was recrystallized twice from acetone and dried over phosphorus pentoxide (mp 89.5–90 °C). The preparations of **1** and maleimides **2b** and **2c** have been described elsewhere.[22] The cholesteryl and cholestanyl esters were prepared from reaction of cholesterol or 3β-cholestanol with the appropriate carboxylic acid chloride in pyridine solution. After filtration of the crude reaction mixture and evaporation of excess pyridine, the products were purified by repeated recrystallization. The melting points and transition temperatures of the mixtures are listed in Table I.

Mixtures of **1** and **2** in the various mesogenic solvents were prepared by dissolving **1** (1 mg, 2.3 × 10^{-6} mol), an equimolar quantity of **2**, and

the mesogen (100 mg) in dichloromethane (2 mL), evaporating the volatile solvent on the rotary evaporator, and then pumping on the residue under high vacuum for 1-2 h. Three portions of the resulting mixture (ca. 25 mg) were placed in tubes constructed from 7-mm Pyrex tubing which had been soaked overnight in 5% aqueous sodium hydroxide, washed repeatedly with distilled water, and oven-dried. The tubes were vacuum-sealed after three freeze-pump-melt degassing cycles. They were placed in the constant-temperature bath for 2 or 4 h (6 or 12 h for **1** + **2c** in S1544), cooled, and then opened. The contents were dissolved in dichloromethane (ca. 1 mL) and analyzed by HPLC. Product yields were determined from the HPLC peak areas (calculated by triangulation), assuming identical detector responses for each set of adducts, and are the averages of three runs each analyzed in triplicate. The isolation and identification of **3-6** from the reaction of **1** and **2a-c** in benzene solution and analytical procedures for their separation and detection have been reported elsewhere.[22]

Acknowledgment. We thank E. Merck (Darmstadt) for the generous gifts of S1409 and S1544. Financial support of this work was provided by the Natural Sciences and Engineering Council of Canada and the Research Corporation.

Registry No. 1, 1059-86-5; **2a**, 941-69-5; **2b**, 58609-75-9; **2c**, 141171-23-5; **3a**, 141197-50-4; **3b**, 112575-19-6; **3c**, 141171-24-6; **4a**, 141171-25-7; **4b**, 112575-18-5; **4c**, 141171-26-8; **5a**, 141171-27-9; **5b**, 112575-20-9; **5c**, 141171-28-0; **6a**, 141171-29-1; **6b**, 141269-54-7; **6c**, 141171-30-4; CnP, 141269-55-8; CnB, 141269-56-9; CnT, 141269-57-0; ChCB, 22575-27-5; S1409, 79709-85-6; S1544, 80955-71-1.

Synthesis of Azapenams, Diazepinones, and Dioxocyclams via the Photolytic Reaction of Chromium Alkoxycarbene Complexes with Imidazolines

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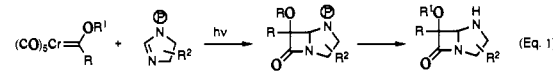
Abstract: Photolysis of chromium alkoxycarbene complexes with *N*-(benzyloxycarbonyl)imidazolines produced protected azapenams. Hydrogenolysis gave free azapenams which were stable, one of which was characterized by X-ray crystallography. Hydrogenolysis under acidic conditions produced hexahydro-1,4-diazepin-5-ones. Treatment of the free azapenams with camphorsulfonic acid produced unsaturated 14-membered tetraazamacrocycles in excellent yield. These were reduced to dioxocyclams.

Introduction

The photolytic reaction of chromium carbene complexes with imines to produce β-lactams has been developed[1] and extensively studied in these laboratories,[2] and a wide range of β-lactam types has been synthesized by this methodology. These include monocyclic β-lactams,[1,3] cephams,[4] oxacephams,[4] carbacephams,[5,6] penams,[5] carbapenams,[5] and (in low yield) oxapenams,[4] many in both the racemic and optically active[7] forms. Noticably absent from this list are azapenams, a relatively rare class of compounds. Although azapen*ems*, having an sp^2 center in the 5-membered ring, have been synthesized by a variety of methods,[8-14] azapen*ams*, from the reaction of azidoketene with imidazolines, have only been detected as intermediates, but not isolated.[15] Because of the mild reaction conditions (visible light, almost any solvent, no other reagents) and the broad scope of the photolytic reaction of chromium carbene complexes with imines to produce β-lactams, azapenams were chosen as suitable targets to test the limits of this methodology (eq 1). Below, the results of studies addressing this issue are reported.



Results and Discussion

Synthesis of Protected Imidazolines. Imidazolines are available by a number of routes,[16] but the reaction of a 1,2-diamine with *tert*-butyl isocyanide with silver cyanide as catalyst[17] proved most

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