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NMR Studies of Selected Cholesteric Compounds†

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Abstract—High resolution NMR spectra of solutions were studied in order to find a possible explanation for the differences in transition temperatures between corresponding esters of cholesterol and thiocholesterol and within each homologous series. In this investigation, only gross changes in chemical shift of resonant lines were utilized to account for the higher thermal stability of the cholesteric mesophase exhibited by sulfur substituted derivatives. The spectra obtained for the solutions clearly demonstrate a decrease of the force constant for the carbonyl group of the thioesters and thereby support the argument that lateral forces may be mainly responsible for higher transition temperatures. However, the data are not sufficient to explain the decrease of thermal stability for the cholesteric mesophase within a homologous series.

Previous studies of homologous series have attempted to correlate mesomorphic behavior with structural features of the molecule. Within a homologous series the transition temperatures are the result of changes in molecular length or size and of polarizability, while for corresponding members of different but comparable series the change of transition temperature is a measure of the chemical influence of the applied substitution. Figure 1[1] presents the experimental data for the homologous alkanoic ester series of cholesterol and thiocholesterol. These data show that the smectic–cholesteric transition temperatures increase for the sulfur substituted compounds. By interpreting the reported spectroscopic evidence for sulfur–oxygen analogues, Elser[2] was led to the conclusion that the sulfur substitution reduces the lateral attraction between molecules and thus

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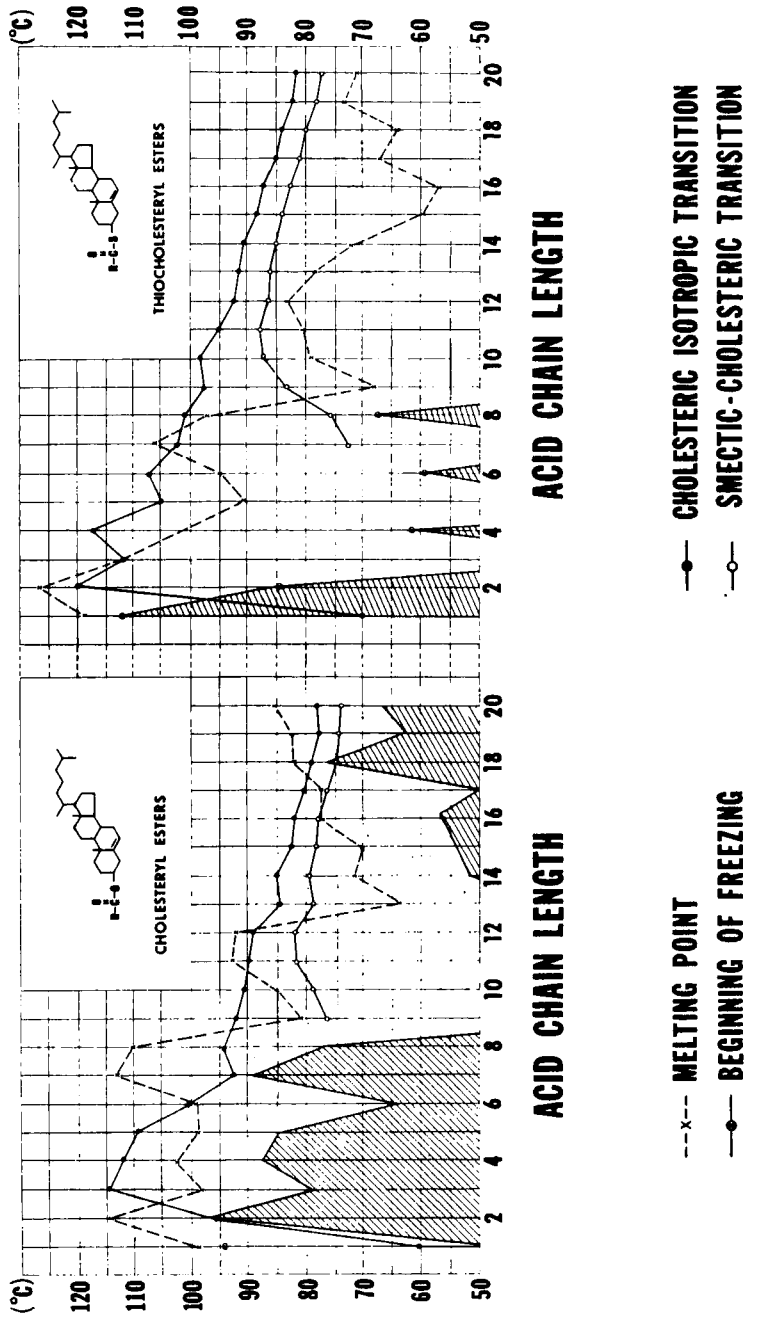

Figure 1. Transition temperatures of the esters of cholesterol and thiocholesterol.

should reduce the smectic–cholesteric temperatures. He also pointed out that this argument is contrary to the customary explanation that a decrease in lateral attraction should manifest itself in a decrease in the smectic–cholesteric transition temperatures. In this study, we wanted to obtain additional experimental evidence which could explain this effect. In addition, we also hoped to find experimental evidence which could explain the increase in the cholesteric–isotropic transition temperatures due to substitutions in general and the unusual and irregular cholesteric isotropic transition temperatures of the formate and thioformate.

A detailed comparison of the data obtained from proton high resolution nuclear magnetic resonance (NMR) of the esters of cholesterol and thiocholesterol was made among and between the members of each series. This investigation did not include complete structure analysis of each spectrum but compared only gross changes in the chemical shift of the resonant lines with known physical properties.

1. Experimental

The spectra were obtained with a Varian HA-100 spectrometer operating at 100 MHz. Chemical shifts of the lines of the sterol esters in deuterochloroform were measured at room temperature in parts per million (ppm) against tetramethylsilane (TMS) as internal standard. Solution strengths ranged from 0.2 to 0.5 molar, with a sample purity of 99%.[2] Selected samples were run without a solvent in the mesomorphic state. Except for expected line broadening, no changes in the NMR spectra were noted.

For examining single proton peaks, time averaging of the spectra was often necessary. However, the system's stability was not adequate for the precision desired, and spectra runs over an hour were distorted due to system drift. To eliminate this problem, a PDP-8 computer was used to maintain system stability and perform the desired time averaging functions.

The PDP-8 Data Processor monitors the shim signal (an indication of field homogeneity) and by servo-drive pots adjusts the " Y " and " Curvature " controls. Thus the system readjusts the field homogeneity to compensate for any instability which may occur.

The versatility of the PDP-8 is apparent considering the variety of functions it performs. It time averages the data collected from computer controlled sweeps, monitors the shim signal, and readjusts the field homogeneity. The data collected can be obtained in either normal spectral output or integral form. Permanent recordings are obtainable in either recorder readouts, teletype printout or paper tape. In addition, a visual readout from an oscilloscope allows quick checks on collected data. More information concerning the electronics, interfacing and results of the computer controlled system will be available in a future publication.[3]

2. NMR Spectrum

Figure 2 exhibits the NMR spectra of cholesteryl acetate, decanoate, and eicosanoate. The four sharp resonant lines that appear at 0.67, 0.82, 0.89, and 1.01 ppm arise from the methyl protons (a), (b), (c), and (d)[4,5] of cholesterol. The protons (b) will show a doublet at 0.82 and overlapping at 0.89 due to coupling with the CH proton ($J = 3.2$ Hz). The methylenic protons (g) resonate around 1.13 ppm. The vinyl proton of cholesterol (f) appears as a broad doublet at 5.36 ppm.[6] Due to its coupling to the protons in ring A of cholesterol, the 3α-proton (e) resonance at 4.57 ppm is theoretically composed of 27 overlapping lines.

In the case of cholesteryl acetate the methyl group of the acetyl moiety (i) appears at 2.00 ppm. For the cholesteryl esters from butyrate to nonadecanoate, the α-methylene group of the acyl moiety appears as a triplet at 2.26 ppm. The methylene groups (h) of the alkyl chain could not be identified for the propionate through hexanoate due to the lines caused by the steroid nucleus, but for the heptanoate to eicosanoate a clear resonant line appears at 1.27 ppm.

Table 1 lists the chemical shifts in parts per million of certain resonant lines for the cholesteryl esters. Except for the formate case, these data indicated that no gross changes in the chemical shift of these protons occur as the chain length for the cholesteryl esters is increased.

Figure 3 depicts the NMR spectra of the acetate, decanoate, and eicosanoate of thiocholesterol. The four sharp resonant lines arising from thiocholesterol are the same as the cholesteryl esters. The

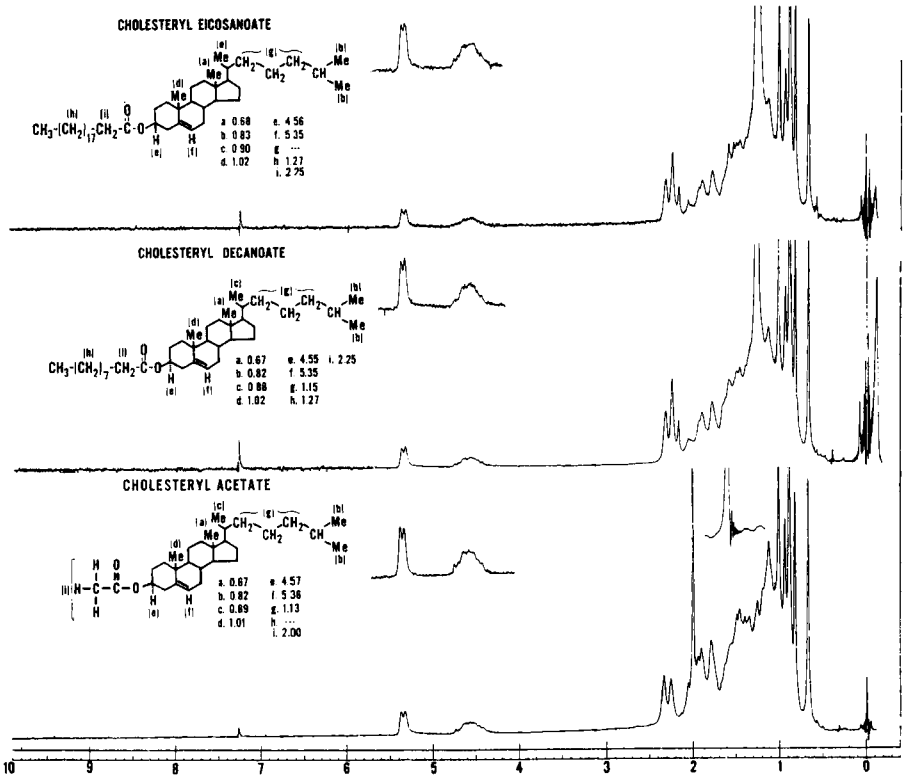

Figure 2. NMR spectra of cholesteryl acetate, decanoate, and eicosanoate.

vinyl proton (f) of thiocholesterol appears as a broad doublet at 5.36 ppm. The 3α-proton (e) resonance at 3.27 ppm is theoretically composed of 27 overlapping lines. In the case of S-cholesteryl thioacetate the methyl group of the acetyl moiety (i) appears at 2.26 ppm, while the α-methylene group of the acyl moiety (i) for all other thiocholesteryl esters appears as a triplet at 2.48 ppm.

The methylene resonance of the acyl group (h) could not be identified for thiopropionate, thiobutyrate and pentanethioate due to lines caused by the steroid nucleus; however, for octanethioate to eicosanethioate its sharp resonant line appears at 1.27 ppm.

Table 2 lists the chemical shifts in parts per million of certain protons for the thiocholesteryl esters. Excluding the thioformate case, these data indicate that no gross changes in the chemical shifts

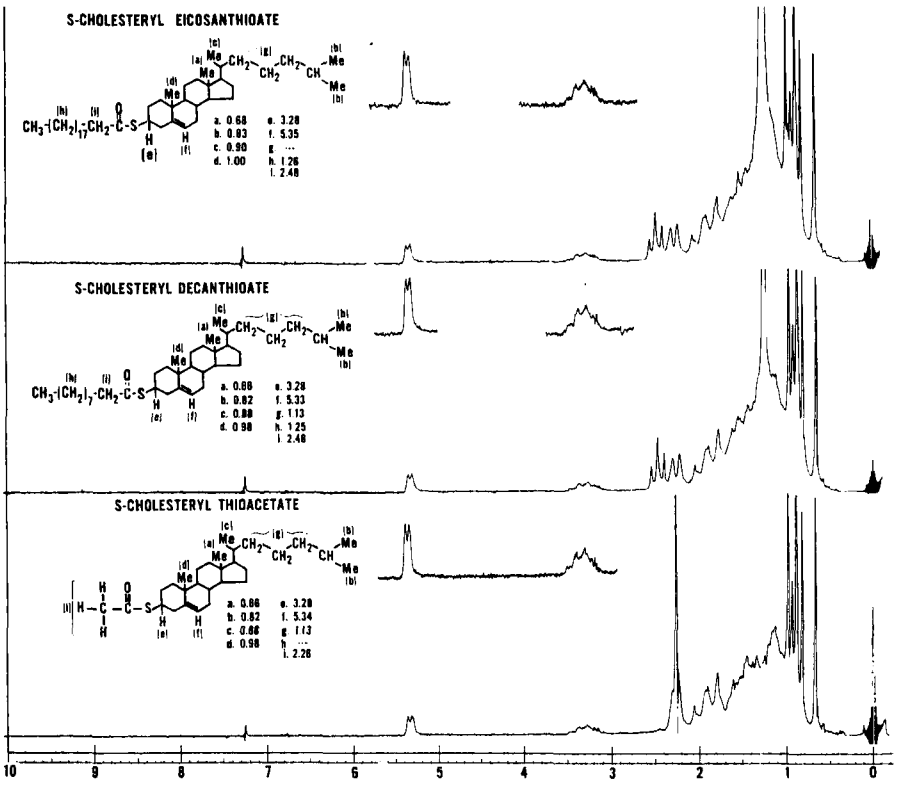

Figure 3. NMR spectra of the acetate, decanoate, and eicosanoate of thiocholesterol.

occur as the chain length is increased. A comparison of the chemical shifts (excluding the formate and thioformate case) listed in Table 1 and Table 2, shows no significant changes except a constant upfield shift of 1.30 ppm for the 3α-proton and a 0.24 ppm constant downfield shift for the α-methylene group of the acyl moiety of the thiocholesteryl esters. This indicates that the 3α-proton of the thiocholesteryl esters is more shielded than that of the cholesteryl esters.

Figure 4 shows the NMR spectra of cholesteryl formate and S-cholesteryl thioformate. By comparing the two spectra, one notices that the cholesterol resonant lines have identical chemical shifts, the 3α-proton (e) shifts 1.20 ppm upfield and the formyl proton (h) shifts downfield by 2.10 ppm for the S-cholesteryl thioformate case.

TABLE 1 Lists of the Chemical Shifts in Parts per Million of Certain Resonant Lines of Cholesteryl Esters

Compound	Line							$(CH_2)_n$	CH_2
	A	B	C	D	E	F	G	H	I
Formate	0.68	0.83	0.90	1.05	4.70	5.39	1.14	8.02	—
Acetate	0.67	0.82	0.89	1.01	4.57	5.36	1.13	—	2.00
Propionate	0.67	0.82	0.88	1.01	4.59	5.37	1.12	—	2.24
Butyrate	0.67	0.82	0.89	1.01	4.62	5.38	1.12	—	2.29
Pentanoate	0.66	0.82	0.88	1.01	4.60	5.37	1.12	—	2.25
Hexanoate	0.68	0.83	0.90	1.02	4.60	5.37	1.14	—	2.26
Heptanoate	0.68	0.83	0.89	1.02	4.58	5.36	1.14	1.28	2.26
Octanoate	0.68	0.83	0.90	1.02	4.60	5.37	1.14	1.28	2.26
Nonanoate	0.67	0.82	0.88	1.01	4.59	5.36	1.13	1.27	2.26
Decanoate	0.67	0.82	0.88	1.02	4.55	5.35	1.15	1.27	2.25
Dodecanoate	0.66	0.82	0.88	1.00	4.60	5.36	1.13	1.25	2.26
Tetradecanoate	0.68	0.83	0.89	1.02	4.60	5.37	1.14	1.26	2.26
Pentadecanoate	0.68	0.84	0.90	1.02	4.60	5.38	1.14	1.26	2.26
Hexadecanoate	0.67	0.82	0.88	1.01	4.58	5.36	1.13	1.25	2.26
Octadecanoate	0.68	0.83	0.90	1.02	4.60	5.38	1.14	1.26	2.26
Nonadecanoate	0.68	0.84	0.89	1.01	4.62	5.38	1.13	1.27	2.26
Eicosanoate	0.68	0.83	0.90	1.02	4.56	5.35	1.13	1.27	2.25

TABLE 2 Lists of the Chemical Shifts in Parts per Million of Certain Resonant Lines of the Esters of Thiocholesterol

Compound	Line							$(CH_2)_n$	CH_2
	A	B	C	D	E	F	G	H	I
Thiocholesterol	0.67	0.83	0.99	1.00	2.63	5.11	1.13	—	—
Formate	0.68	0.84	0.90	1.01	3.50	5.36	1.14	10.12	—
Acetate	0.66	0.82	0.88	0.98	3.28	5.34	1.13	—	2.26
Propionate	0.67	0.83	0.89	0.99	3.20	5.36	1.15	—	2.52
Butyrate	0.68	0.83	0.90	1.00	3.30	5.36	1.13	—	2.48
Pentanoate	0.68	0.84	0.94	1.00	3.31	5.37	1.15	—	2.49
Octanoate	0.68	0.84	0.90	1.00	3.30	5.37	1.16	1.29	2.50
Nonanoate	0.68	0.84	0.90	1.00	3.30	5.36	1.15	1.27	2.49
Decanoate	0.66	0.82	0.88	0.98	3.28	5.33	1.13	1.29	2.49
Undecanoate	0.68	0.84	0.90	1.00	3.30	5.37	1.16	1.28	2.50
Dodecanoate	0.69	0.84	0.92	1.02	3.33	5.38	1.18	1.28	2.50
Pentadecanoate	0.68	0.84	0.90	1.00	3.30	5.36	1.17	1.27	2.50
Hexadecanoate	0.69	0.84	0.91	1.00	3.32	5.36	1.16	1.28	2.49
Heptadecanoate	0.68	0.84	0.99	1.00	3.34	5.37	1.16	1.27	2.50
Eicosanoate	0.68	0.83	0.90	1.00	3.28	5.35	1.17	1.26	2.48

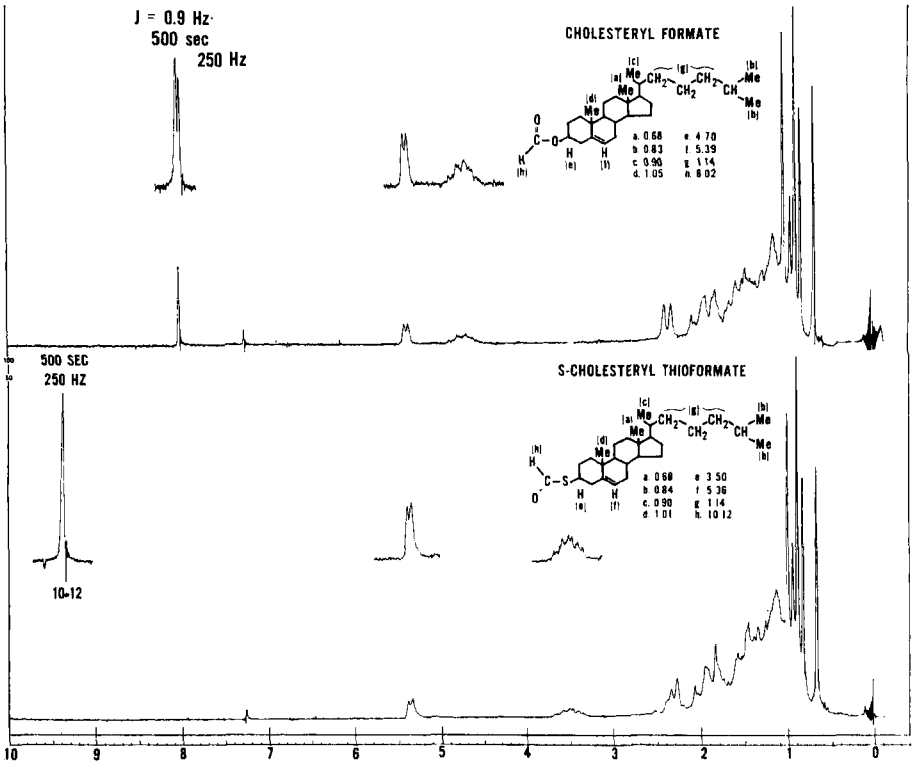

Figure 4. NMR spectra of cholesteryl formate and S-cholesteryl thioformate.

However, the formyl proton exhibits a singlet for S-cholesteryl thioformate and a doublet for cholesteryl formate. In the cholesteryl case, the formyl proton is coupled to the 3α-proton with a coupling constant of 0.9 Hz. A similar coupling is found for cyclohexyl formate and corresponds with the values for long range coupling constants in alkyl formates as reported by Hayamizu and Yamamoto.[7] For cholesteryl acetate, the acetyl group is not coupled to the 3α-proton (Fig. 2).

Due to the resonance energy of the ester functionality the C—O bond has a partial double bond character and only the *cis* and *trans* positions are favored. In this case the preferred conformation of the carbonyl is *cis* to the 3α-proton. Karabatsos *et al.*[8] have reported that the *cis* conformation of ethyl formate is favored over the *trans*

by 2.4 Kcal/mole as compared to 0.6 Kcal/mole for ethyl acetate. The preferred arrangement of the carbonyl group for cholesteryl formate might explain the 35 °C difference in clearing point between cholesteryl formate and cholesteryl acetate. On substitution of oxygen by sulfur, the bond angle decreases from 110° for the C—O—C bond to 104° for the C—S—C bond, while the bond length increases from 1.3 Å for the C—O bond to 1.7 Å for the C—S bond. This could explain the absence of long range coupling of the formyl proton to the 3α-proton of S-cholesteryl thioformate due to the increase in separation between the carbonyl group and the sterane moiety.

3. Conclusion

A comparison of major changes in the spectra was unable to explain the decrease in thermal stability of the cholesteric mesophase with an increase in chain length. By possibly substituting C^{13} and F^{19} at appropriate positions in the molecule and studying their spectra, additional insight might be gained concerning this problem. Except for the formate and thioformate case, no major unexplainable changes in any of the resonant lines occur as the chain length for the two homologous series is increased.

We know that replacing of the oxygen in cholesteryl esters with sulfur results in an increase of the smectic-cholesteric and the cholesteric-isotropic transition temperatures. There is an increase in the shielding (excluding the formates) of the 3α-proton as indicated by a 1.30 ppm upfield shift for the proton in thiocholesteryl esters. There is a decrease in the shielding of the α-methylene group on the carbonyl which shows a 0.24 ppm downfield shift for the thiocholesteryl esters.

Inductive and resonance effects are important in interpreting the effects of the oxygen and the sulfur atom in the ester series. Since the electronegativity of oxygen is higher than that of sulfur the inductive effect of oxygen which increases the carbonyl force constant in ordinary esters will be greater than a similar inductive effect of sulfur in thio esters.

There also appears to be a greater tendency toward overlap of the carbonyl carbon π electron with a non-bonding electron pair of the sulfur atom than with a non-bonding electron pair of an oxygen atom.

A competition between the non-bonding electron pair of sulfur and the carbonyl oxygen π electron for overlap with the carbonyl carbon π electron should cause a smaller carbonyl force constant for the thio esters.[9] This has been shown from the infrared data of the carbonyl stretching frequencies.[9,10] The carbonyl stretching frequencies for the aliphatic thio esters are ~ 1690 cm^{-1} as compared to ~ 1735 cm^{-1} for the aliphatic esters.

A special case which supports this theory is the comparison of the NMR spectra of cholesteryl thioformate and cholesteryl formate. The data show that the formyl proton becomes less shielded (shifts

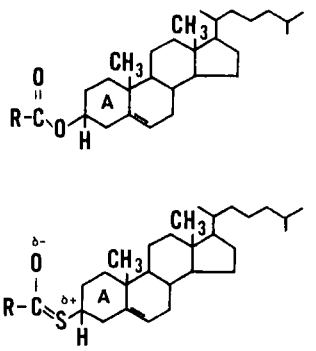

Figure 5. Schematic drawing of esters of cholesterol and thiocholesterol indicating the relative charge distribution.

downfield by 2.10 ppm) and the 3α-proton becomes more shielded (shifts upfield by 1.20 ppm).

Figure 5 is a schematic drawing indicating the relative charge distribution for the two homologous series. This charge distribution has also been proposed by Janssen and Sandström.[11] These data indicate a decrease in the force constant of the carbonyl groups, thus implying an increase of the lateral interactions between the molecules for the thiocholesteryl esters. This supports the arguments put forth by Gray,[12] that the increase of lateral attraction between molecules are mainly responsible for the increase of the thermal stability of the smectic phases. Therefore, this increase of lateral attraction between molecules may possibly be used to explain the increase of the thermal stability of the cholesteric mesophase.

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