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# INTERACTION OF LANTHANIDE SHIFT REAGENTS WITH 5-R-3-THIAZOLYLCHROMONES. SLOW EXCHANGE IN THE LSR-SUBSTRATE COMPLEX

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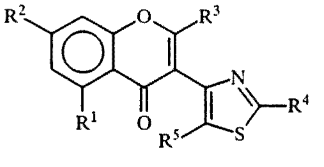
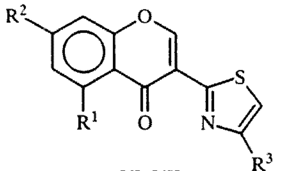
*The interaction of Eu(FOD)$_3$ with 5-substituted 3-hetarylchromones has been studied. It has been shown that the nature of the substituent at position 5 of the chromone nucleus affects the direction of coordination of the LSR and the rate of exchange between coordinated and free substrate molecules. The latter caused large exchange broadening of those signals for which a large lanthanide induced shift was observed. Complex formation with the LSR may change the conformational composition of substrate molecules and lead the molecule to change to a conformation which reacts more effectively with the LSR. Exchange broadening is explained by chelation of the LSR by the bidentate substrate molecule.*

We have previously studied the interaction of lanthanide shift reagents (LSR) with 2- and 3-hetarylchromones and have shown that conclusions on the structure and conformation of these molecules in solution can be drawn from the size of the lanthanide induced shifts (LIS) [1-3]. Both 2- and 3-hetarylchromones react effectively with LSR via the unshared pairs of the carbonyl oxygen in the chromone ring or of the pyridine type nitrogen in the heterocyclic substituent. Steric hindrance near the carbonyl weakened coordination or lead to a change in the coordinating center of the substrate molecule.

However, as a rule steric hindrance near the coordinating center of the molecules did not affect the rate of exchange between coordinated and free substrate molecules. Consequently, larger or smaller LIS are observed in the $^1$H NMR spectra modified by LSR depending on the effectiveness of the coordinating centers of the substrate molecules, but exchange broadening is absent. In the present work we observed unexpected broadening in the $^1$H NMR spectra of 5-substituted 3-thiazoylchromones in the presence of Eu(FOD)$_3$. These compounds, unlike other derivatives, have bulky substituents close to the chromone carbonyl group and consequently their complexation with LSR is different in a number of ways. We have studied the 3-thiazolylchromones I-VII which contain CH$_3$, OCH$_3$, OH and OCOCH$_3$ groups in the 5 position of the chromone ring.



I–V



VI, VII

I $R^1 = R^3 = R^4 =$ Me, $R^2 = OCOCH_3$, $R^5 =$ H; II $R^1 = R^4 =$ Me, $R^2 = OCH_3$, $R^3 = R^5 =$ H; III $R^1 = OCH_3$, $R^2 = R^4 =$ Me, $R^3 = R^5 =$ H; VI $R^1 = OCOCH_3$, $R^2 =$ Me, $R^3 = R^5 =$ H, $R^4 =$ Ph; V $R^1 = OCOCH_3$, $R^2 = R^4 = R^5 =$ Me, $R^3 =$ H, $R^4 =$ Ph; VI $R^1 = R^3 =$ Me, $R^2 = OCOCH_3$; VII $R^1 =$ OH, $R^2 = R^3 =$ Me

The values observed for specific LIS are given in Table 1.

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TABLE 1. Induced Shifts of the Proton Signals of 3-Thiazolylchromones

| Compound | Signals of chromone fragment | | | | | Signals of thiazole ring | | |
|---|---|---|---|---|---|---|---|---|
| | 2-R | 5-R | 6-H | 7-R | 8-H | 2'-R | 4'-R | 5'-R |
| I | $CH_3$, 0,3 | $CH_3$, 24,4 | 2,7 | OAc, 0,3 | 1,6 | $CH_3$, 10,2 | — | H, 1,3 |
| II | H, -0,9 | $CH_3$, 30,6 | 3,6 | $OCH_3$, 0,6 | 0,1 | $CH_3$, 15,4 | — | H, -0,3 |
| III | H, -0,9 | $OCH_3$, 23 | 9,7 | $CH_3$, 2,2 | 2,2 | $CH_3$, -0,1 | — | H, -2,7 |
| IV | H, 0,5 | OAc, 2,1 | 1,1 | $CH_3$, 0,2 | 0,7 | Ph, 0,2 | — | H, 0,3 |
| V | H, 1,1 | OAc, 1,4 | 0,2 | $CH_3$, 0,5 | 0,1 | $CH_3$, 3,2 | — | $CH_3$, 3,6 |
| VI | H, -0,5 | $CH_3$, 9,7 | 3,3 | OAc, 0,8 | 0,6 | — | $CH_3$, 18,9 | H, 0,6 |
| VII | H, 0,3 | OH, 13,2 | 2,0 | $CH_3$, 0,5 | 0,3 | — | $CH_3$, 12,4 | H, 2,4 |

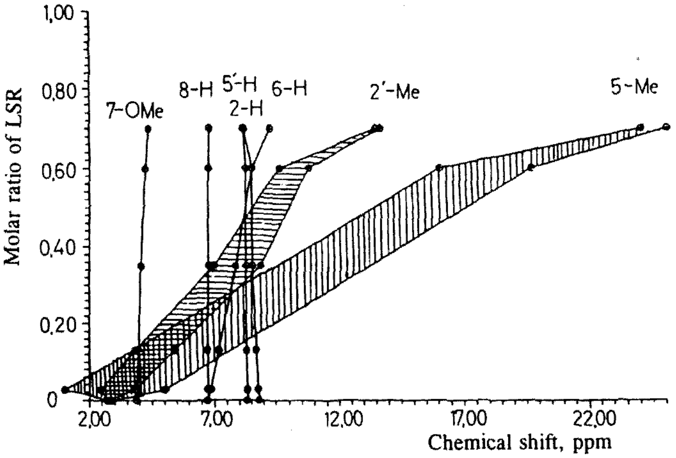

Fig. 1. Dependence of the value of the $^1H$ NMR chemical shift for compound II on the LSR-substrate ratio. The shaded areas correspond to the observed width of the signals.

The interactions of the LSR with compounds I-III and VI-VII are unexpected. A number of signals are strongly broadened on the addition of a very small amount of Eu(FOD)3. The signals of the 5-$CH_3$ and 2'-$CH_3$ groups of compounds I and II are broadened, while for compound III the 5-$OCH_3$ and 6-H signals are broadened, while for compounds VII and VII it is the signals of 4'-$CH_3$ and the substituent at position 5 of the chromone ring which are broadened. No broadening is observed for the remaining proton signals but the values of their LIS are also small. For some LSR-substrate ratios the broadening is so large that the signals disappear. This is illustrated in Fig. 1 in which the change in the spectrum of II under the influence of the LSR is shown schematically. The shaded areas correspond to the broadening of the signals of the 5-$CH_3$ and 2'-$CH_3$ groups. The signals show greatest broadening with small LSR content: at this stage they are 6-7 ppm wide. The signals narrow as the amount of LSR increases until the anomalous broadening virtually disappears at an equimolar ratio of LSR to substrate.

The line broadening can be either paramagnetic or exchange in nature. To elucidate this we studied the effect on the spectra of changing the temperature from 297 to 337 K. A three-dimensional diagram of the 6-H signal of compound III at various temperatures and LSR-substrate ratios is shown in Fig. 2. The half-width of the signal is given on the vertical axis while the temperature and the LSR-Substrate molar ratio are shown on the other two axes. The greatest half-width of the signal (18 Hz) is observed at a LSR-substrate ratio of 0.1. On increasing the temperature the signal narrowed almost to the natural

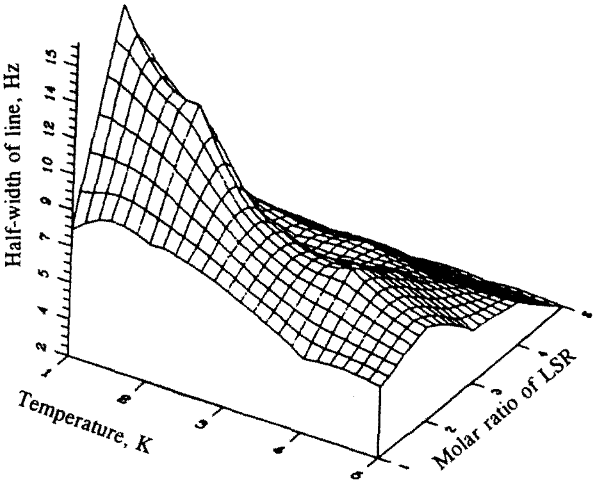

Fig. 2. Dependence of the half-width of the 6-H proton signal for compound III on the LSR-substrate ratio and the temperature. The LSR-substrate ratios, indicated by numbers 1-5, are 0.033, 0.1, 0.2, 0.5 and 0.9. The temperatures, indicated by number 1-5, are 297, 307, 317, 327 and 337 K.

width of a signal with a coupling constant of about 2 Hz. The width of the proton signal of the 5-$OCH_3$ group changes similarly but its broadening is greater by about an order of magnitude. At 337 K the spectrum is normal for spectra modified by an LSR.

The way in which the spectra of compounds I-III, VI and VII vary with temperature in the presence of the LSR shows that the broadening is caused by exchange since paramagnetic broadening changes in parallel with the size of the LIS and is extinguished at high temperature only when the LIS decreases to zero. In our examples considerable values of the LIS remain at high temperatures while the broadening disappears completely.

Comparison of the LIS values for compounds I-III, VI and VII shows that the nature of the 5-R substituent may have a considerable effect on the coordination of the molecule with the LSR. For example, considerable LIS are observed for both the 5-R substituent and the methyl group in the thiazole ring for compounds I, II, VI and VII. This indicates that both the chromone carbonyl and the thiazole nitrogen take part in complex formation. The thiazole unit is oriented so that the two coordination centers of the molecule are optimally close. The thiazole ring is in a *Z* conformation relative to the bond between the heterocyclic units. We attempted to determine the structures of the adducts of compounds I and II with the LSR by method [4] assuming a pseudocontact model of the interaction. Variations of the calculation were carried out assuming that the coordination center was the chromone carbonyl, the thiazole nitrogen or both to an equal degree. It was impossible to get good agreement between the calculated and observed LIS with any of these calculations (it is likely therefore that complex formation involves both coordination centers, but to an unequal extent).

The interaction of the LSR with compound III is quite different. In this case the 2′-methyl signal is neither shifted nor broadened while the 5′-H signal has a considerable LIS to high field, which indicates that the thiazole unit is oriented so that the 5′-H proton is directed toward the chromone ring, i.e., thiazole ring is in the *E*-conformation and the thiazole nitrogen cannot coordinate with the LSR. The large LIS and broadening of the 6-H proton signal shows that the methoxyl oxygen takes part in complex formation in this case. Calculation showed that the best correlation between experimental and calculated LIS was obtained if it was assumed that the principal magnetic axis in the adduct was directed toward the methoxyl oxygen atom. The sum of the mean squared deviations of the calculated LIS from the experimental values did not exceed 0.1 in this case which shows that the chosen model for complex formation corresponds with experiment.

Comparison of the structures of compounds III and II shows that they differ only in the substituents in the benzene ring of the chromone unit. The nature and size of these substituents cannot have a marked effect on the mutual orientation of the heterocyclic units. Nevertheless, according to the results obtained with the LSR, the orientations of the thiazole units in these molecules are not the same, i.e., the LSR influences the structure of the substrate to which it is bonded. Since molecular mechanics calculations show that the planar conformations of II and III are similar in energy with a small barrier to transformations between them, addition of the LSR leads to stabilization of the conformation which interacts more effectively with $Eu(FOD)_3$.

Coordination of the LSR with compounds IV and V, with acetyl groups in position 5 of the chromone ring, is quite different. The LIS values for all signals are small and no anomalous broadening is observed. The largest LIS occur for the acetyl group and the methyl group close to the thiazole ring. Apparently the carbonyl oxygen of the chromone ring is unable to complex with the LSR because of steric hindrance and coordination, though weak, occurs at the 5-acetyl group and the thiazole nitrogen.

Comparison of the values of the LIS for compounds I-III, VI and VII with the corresponding values for other 3-hetarylchromones [1-3] shows that values of the induced shifts for 5-H proton signals are considerably smaller for derivatives of benzofuran, benzodioxane and furan than for compounds I-V although the latter contain 5-R substituents which hinder coordination with the LSR. Increased LIS indicate increasingly effective interaction with the LSR molecule. The only explanation is the formation of chelated adducts which are considerably more stable than adducts of the LSR with monodentate ligands. Increased LIS on chelate formation has been noted earlier in a number of cases [5]. Formation of unusually stable adducts with the LSR explains the origin of line broadening in the spectra of compounds I-III, VI and VII in the presence of the LSR. Line broadening is linked to slow exchange between uncoordinated substrate molecules and molecules which have formed chelates with the LSR.

Thus in hetarylchromones with carbonyl groups sterically hindered by substituents at position 5 of the chromone ring the direction of coordination of the LSR is determined by the size and nature of this substituent and the structure of the heterocyclic ring. The presence of a substituent containing an alternative center for coordination with the LSR may cause a decrease in the rate of exchange between coordinated and free substrate molecules and consequently to exchange broadening of signals with large lanthanide induced shifts.

## EXPERIMENTAL

$^1H$ NMR Spectra of 3-thiazoylchromones were measured with a Bruker WP 100-SY instrument at 100 MHz. Commercial $Eu(FOD)_3$ was used without further purification. Molecular mechanics calculations were carried out with the PCMODEL program and experimental results were treated with the GRAFER and SURFER programs.

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