Chemistry of Heterocyclic Compounds, Vol. 33, No. 12, 1997

DETECTION OF THE CHIRALITY OF 3-HETEROARYL-CHROMONES USING LANTHANIDE SHIFT REAGENTS

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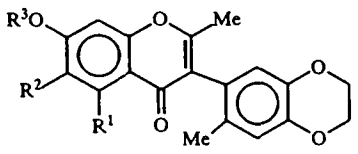
A study was carried out on the reaction of chiral benzodioxane, benzofuran, and thiazole derivatives of isoflavone with various lanthanide shift reagents (LSR). The PMR shifts depend on the LSR used, while detection of chirality for these compounds using chiral LSR was difficult. Lowering the temperature and adding Yb(FOD)$_3$ may enhance the splitting of the PMR signals of chiral molecules in the presence of LSR.

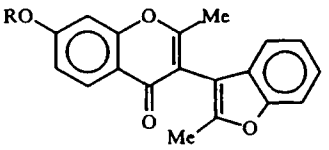
3-Heteroarylchromones containing substituents near the axis of fusion of the heterocyclic rings may exist as a racemic mixture of two optical antipodes (atropoisomers) [1-3]. Detection of the chirality of these compounds is quite feasible using a lanthanide shift reagent (LSR), namely, Eu(HFBC)$_3$, which contains a (+)-D-camphor residue [4]. A pair of diastereomeric adducts is formed upon coordination of the chiral LSR and substrate racemate. The PMR spectrum of this pair shows splitting of individual signals. Such splitting is evidence for the chirality of the compound studied. The magnitude of the splitting of the signals is a function of the capacity of the individual electron-donor groups of the substrate molecule to coordinate with the LSR, the LSR/substrate mole ratio, and temperature for measurement of the spectrum. Thus, interest was found in a study of the conditions, at which maximum splitting is found in such PMR spectra.

For this purpose, we investigated the reaction of the shift reagent, Eu(HFBC)$_3$ with I-VIII, which contain various heterocyclic substituents:



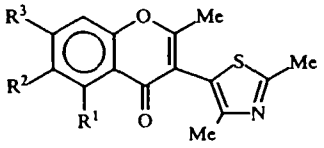
I-III

I R^1 = H, R^2 = Et, R^3 = Me; II R^1 = OH, R^2 = H, R^3 = Me; III R^1 = OCOMe, R^2 = H, R^3 = COMe



IV, V

IV R = $PhCH_2$; V R = C_3H_7



VI-VIII

VI R^1 = H, R^2 = Me, R^3 = OMe; VII R^1 = H, R^2 = Me_3, R^3 = OCOMe; VIII R^1 = OH, R^2 = H, R^3 = Me

Chirality was previously detected for compounds with similar structure [1-3]. The presence of substituents such as OH and OCOMe at $C_{(5)}$ of the chromone system hinders coordination with LSR. Lanthanide-induced shifts (LIS) and splitting of the signals are not observed in the PMR spectra of these compounds (II, III, and VIII) despite their chirality. LIS are observed for the other compounds studied. The magnitudes of these LIS at room temperature are given in Tables 1-5. The LIS obtained for the adducts with achiral LSR, Eu(FOD)$_3$ and Yb(FOD)$_3$, are also given. The individual LIS, i.e., the shifts calculated for

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 0009-3122/97/3312-1456$18.00

TABLE 1. Lanthanide-Induced Shifts Obtained for Benzodioxane Derivative I

LSR	2-Me	5-H	6-CH_2	6-Me	7-OMe
Eu(HFBC)$_3$	1,21 1,12	2,56 2,31	−0,44	−0,23 −0,37	0,14
Eu(FOD)$_3$	1,2	4,4	0,1	0,1	0,3
Yb(FOD)$_3$	5,6	14,8	1,7	1,6	1,0

LSR	8-H	2'-,3'-CH_2	4'-H	6'-Me	7'-H
Eu(HFBC)$_3$	0,91 0,82	0,2	1,68 1,63	1,12 1,07	0,65 0,47
Eu(FOD)$_3$	0,9	0,2	3,2	2,5	1,4
Yb(FOD)$_3$	3,4	1,0	6,9	9,5	3,3

TABLE 2. Lanthanide-Induced Shifts Obtained for Benzofuran Derivative IV

LSR	2-Me	5-H	6-H	7-OCH_2	8-H	2'-Me	4'-H
Eu(HFBC)$_3$	1,42 1,33	0,48 0,1	−0,7	0	0,7	1,0 0,94	1,8
Eu(FOD)$_3$	3,1	5,2	0	0,3		3,1	3,3
Yb(FOD)$_3$	13,2	19,6	−2,7	1,3	7,5	19,1	12,7

TABLE 3. Lanthanide-Induced Shifts Obtained for Benzofuran Derivative V

LSR	2-Me	5-H	6-H	7-OCH_2	8-H	2'-Me	4'-H
Eu(HFBC)$_3$	2,2 2,1	0,1 0,6	−1,3	0	1,2	2,0 2,1	2,2
Eu(FOD)$_3$	2,6	4,4	0	0,3	1,3	2,6	3,1
Yb(FOD)$_3$	10,0	15,5	−1,9	1,0	5,6	14,7	10,2

an LSR/substrate ratio of 1:1, are presented. These results indicate that the LIS values for the corresponding protons of different compounds upon interaction with the same LSR are similar but the splitting of the signals in the presence of Eu(HFBC)$_3$ differ rather considerably. The greatest splittings were found for compounds with bicyclic heterocycles as substituents in the chromone system. The splittings for the thiazole derivatives are much smaller. This discrepancy is probably related to the topological asymmetry parameters of these molecules [5]. The greatest splitting in all the compounds studied was found for the 5-H, which is closest to the site of coordination with the LSR. Thus, the difference in the chemical shifts of the 5-H signal in diastereomeric adducts for benzodioxane derivatives with sufficient LSR/substrate ratio is 0.3 ppm. A study of thiazole derivatives VI and VII showed that it is quite difficult to detect their chirality at room temperature. The addition of Eu(HFBC)$_3$ leads only to shifts of the PMR signals and broadening of the signal for the chromone 5-H. Significant splitting of the 5-H signal is found only for LSR/substrate ratios above 0.5. Significant changes occur in the spectra when the temperature of the solution is lowered. Thus, all the signals except for the methoxy group singlet are split into two components when the temperature is lowered from 300 K to 290 K. Further cooling to 260 K leads to a greater difference in the chemical shifts between the components of the split signals. Such changes are graphically illustrated in Fig. 1, which gives a three-dimensional diagram with the splitting of the 5-H signal of VI on the vertical axis and Eu(FOD)$_3$/substrate ratio and sample temperature on the other two axes. An increase in the amount of LSR used at room temperature (300 K) generally gives a negligible effect and leads only to a slight increase in splitting. On the other hand, lowering the temperature leads to greater effects. The signal splitting may increase several-fold. Thus, detection of chirality is best carried out at 260-280 K.

Comparison of the effect of different LSR on these PMR spectra shows that the greatest LIS are found for adducts with Yb(FOD)$_3$, for which the 5-H signal may be shifted by several tenths ppm. However, signal broadening is observed even for LSR/substrate mole ratios of 0.1-0.2, which completely hides their multiplicity.

The LIS values found for the ytterbium LSR, which are larger than those found for Eu(HFBC)$_3$, suggest the possibility of enhancing the signal splitting by using both these LSR. Since rapid exchange occurs between the coordination and noncoor-

TABLE 4. Lanthanide-Induced Shifts Obtained for Thiazole Derivative VI

LSR	2-Me	5-H	6-Me	7-OMe	8-H	2'-Me	4'-Me
Eu(HFBC)$_3$	2,0	2,0 2,1	1,9	0,1	0,7	0,6	-0,8
Eu(FOD)$_3$	2,1	4,2	-0,1	0,3	1,0	1,5	1,9
Yb(FOD)$_3$	4,9	16,3	-0,9	1,4	4,0	3,2	9,7

TABLE 5. Lanthanide-Induced Shifts Obtained for Thiazole Derivative VII

LSR	2-Me	5-H	6-Me	7-OCOCH$_3$	8-H	2'-Me	4'-Me
Eu(HFBC)$_3$	0,7	1,4 1,2	1,5	0,1	0,6	0,7	0,5
Eu(FOD)$_3$	3,0	4,7	0,3	1,0	1,2	1,4	1,7
Yb(FOD)$_3$	6,3	12,3	-0,8	2,1	3,9	3,4	10,9

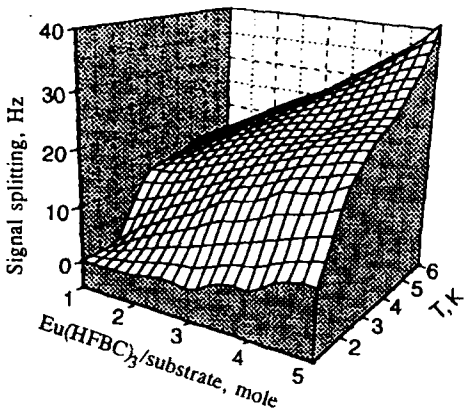

Fig. 1. Dependence of the 5-H signal of VI on temperature and the Eu(HFBC)$_3$/substrate ratio indicated by numbers. On the temperature scale: *1*) 310 K, *2*) 300 K, *3*) 290 K, *4*) 280 K, *5*) 270 K, and *6*) 260 K. On the LSR/substrate ratio scale *1*) 0.12, *2*) 0.21, *3*) 0.3, *4*) 0.38, and *5*) 0.46.

dinated substrate molecules, if the complexation constants of the substrate with various LSR do not differ too much, we might expect an increase in signal splitting. Figure 2 shows the dependence of the chemical shift for 5-H in I (the center of the split signal, Fig. 2*a*) and its splitting (Fig. 2*b*) on the mole ratio of substrate and the two LSR. The addition of Yb(FOD)$_3$ to the adduct of I with Eu(HFBC)$_3$ leads to a considerable increase in the LIS, but the LIS does not reach the values found for the pure adduct with Yb(FOD)$_3$ (Fig. 2*a*). The signal splitting in this diagram corresponds to a surface with a minimum. This behavior indicates that LSR mole ratios exist at which splitting of the 5-H signal is maximal. Thus, in the case of 0.3 mole Yb(FOD)$_3$ and 0.6 mole Eu(HFBC)$_3$ per mole substrate, the splitting reaches 35 Hz, which is 30% greater than for the pure adduct of I with Eu(HFBC)$_3$ for the optimal LSR/substrate ratio. Diagrams similar in form were obtained for the signal of the 7'-Me group in I.

Thus, the combined use of chiral and achiral LSR permit us to enhance the splitting in the PMR spectra of I. However, this method is not general. Use of this approach for thiazole derivatives IV and V are ineffective due to the observed exchange broadening of the signals.

EXPERIMENTAL

The PMR spectra were taken on a Bruker WP 100-SY spectrometer at 100.13 MHz with TMS as the internal standard.

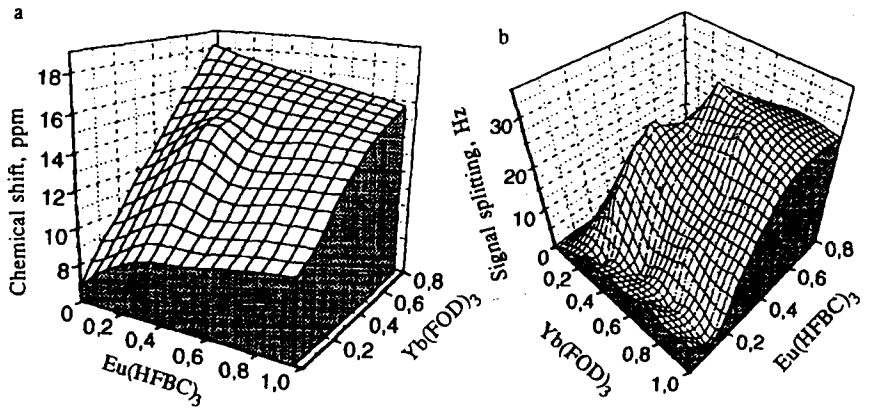

Fig. 2. Dependence of the chemical shift (*a*) and splitting of the signal for 5-H (*b*) in I on the content of $Eu(HFBC)_3$ and $Yb(FOD)_3$.

The syntheses of I and IV-VIII have been described in our previous work [2, 6, 7].

α-(7-Methyl-6-benzodioxan-1,4-yl)-2,4,6-trihydroxyacetophenone (II) was obtained under conditions of the Hesch reaction analogously to α-(7-methyl-6-benzodioxan-1,4-yl)-2,4-dihydroxy-5-ethylacetophenone described in our previous work [2].

2-Methyl-3-(7-methyl-6-benzodioxan-1,4-yl)-5,7-diacetoxychromone (III). A mixture of 3.16 g (10 mmoles) α-(7-methyl-6-benzodioxan-1,4-yl)-2,4,6-trihydroxyacetophenone, 6.4 ml (70 mmoles) acetic anhydride, and 8.4 ml (60 mmoles) triethylamine was maintained for 20 h at 125-130°C. The reaction mixture was then added to ice water containing 1.7 ml (70 mmoles) hydrochloric acid. The precipitate was filtered off, thoroughly washed until there was no odor, and crystallized from 1:1 CCl_4–cyclohexane to give 2.3 g (56%) III, mp 70-72°C. PMR spectrum in $CDCl_3$: 7.21 (1H, d, ^4J = 2.5 Hz, 6-H), 6.80 (1H, d, 8-H), 6.77 (1H, s, 5′-H), 6.59 (1H, s, 8′-H), 4.24 (4H, s, 2′-, 3′-CH_2), 2.36 (3H, s, 5-$OCOCH_3$), 2.34 (3H, s, 7-$OCOCH_3$), 2.16 (3H, s, 2-CH_3), 2.00 ppm (3H, s, 7′-CH_3). Found: C, 64.9; H, 4.6%. Calculated for $C_{23}H_{20}O_8$: C, 65.1; H, 4.7%.

2-Methyl-3-(7-methyl-6-benzodioxan-1,4-yl)-5,7-dihydroxychromone (IX). A sample of 8 ml 5% aq. NaOH was added to a hot solution of 2.1 g (5 mmoles) III in 25 ml ethanol and the reaction mixture was heated at reflux for 3 min. Then, 40 ml water was added and the mixture was heated at reflux for an additional 10 min. Dilute hydrochloric acid was added to the reaction mixture to bring it to pH 4-5. The product was filtered off, washed with water, and dried to give 1.3 g (83%) IX, mp 125-126°C as colorless needles. PMR spectrum in DMSO-d_6: 12.92 (1H, s, 5-OH), 10.83 (1H, s, 7-OH), 6.78 (1H, s, 5′-H), 6.64 (1H, s, 8′-H), 6.35 (1H, d, ^4J = 2.5 Hz, 8-H), 6.19 (1H, d, 6-H), 4.23 (4H, d, 2′, 3′-CH_2), 2.12 (3H, s, 2-CH_3), 1.94 ppm (3H, s, 2′-CH_3). Found: C, 66.8; H, 4.6%. Calculated for $C_{19}H_{16}O_6$: C, 67.1; H, 4.7%.

2-Methyl-3-(7-methyl-6-benzodioxan-1,4-yl)-5-hydroxy-7-methoxychromone (II). A sample of 0.8 g (6 mmoles) freshly calcined potassium carbonate and 0.23 ml (2 mmoles) dimethyl sulfate were added to a solution of 0.62 g (2 mmoles) IX in 30 ml absolute DMF. The mixture was heated at reflux for 25 h and the precipitate was filtered off. Several drops of acetic acid were added to the filtrate, which was then evaporated to dryness. The residue was crystallized from 1:1 ethanol–water to give 0.3 g (45%) II, mp 85-86°C as colorless needles. PMR spectrum in $CDCl_3$: 12.87 (1H, s, 5-OH), 6.80 (1H, s, 5′-H), 6.63 (1H, s, 8′-H), 6.37 (2H, d.d, 6-, 8-H), 4.25 (4H, s, 2′, 3′-CH_2), 3.87 (3H, s, 7-CH_3), 2.19 (3H, s, 2-CH_3), 2.05 ppm (3H, s, 7′-CH_3). Found: C, 71.3; H, 5.2%. Calculated for $C_{20}H_{18}O_6$: C, 71.0; H, 5.3%.

The authors express their gratitude to the INTAS program and International Soros ISSEP program (Grant No. SPU063069) for financial support of this work.

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