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FEATURES OF THE REACTION OF HETEROCYCLIC ANALOGS OF 2'-ALKOXY-CHALCONES WITH LANTHANIDE SHIFT REAGENTS

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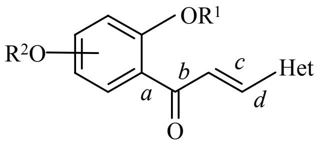
The reaction of lanthanide shift reagents with the heterocyclic analogs of substituted 2'-alkoxychalcones was studied. It was shown that the coordination of Eu(fod)$_3$ and Yb(fod)$_3$ with them takes place in different ways. The former forms mainly adducts of the chelate type with participation of the oxygen atoms of the carbonyl and alkoxyl groups in coordination, while from the latter only the adduct at the carbonyl group is obtained. For this reason it was concluded that there are some limitations to the use of the reagents for conformational analysis of organic compounds. It was shown that they can only be used to study the conformational movements of the molecules not affecting the complexation process.

Keywords: heterocyclic analogs of chalcones, lanthanide shift reagents, configuration, lanthanide-induced shifts.

Lanthanide shift reagents (LSR) make it possible to obtain extremely useful information on features of the structure of a molecule in solution [1, 2]. However, individual aspects of the reaction of the LSR with organic donor molecules have so far been insufficiently studied. In particular, this concerns their coordination with bifunctional compounds, which include chalcones and their heterocyclic analogs (physiologically active substances and synthons for the production of various flavonoids and isoflavonoids [3-5]. In view of the importance of the compounds a series of papers have been devoted to determination of details of their structure [6-9]. In spite of the simplicity of the molecule of chalcone or its analogs with general formula **1**, on account of the presence of the enone fragment containing three single bonds (*a*, *b*, and *d*) the existence of eight planar conformers is possible. The realization of one or the other conformer can be determining in the biological activity of these substances. Compounds of type **1** can be investigated by means of lanthanide shift reagents.



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Het = 2-thiazolyl, 2-benzofuryl, 2-pyridyl; R^1 = CH$_2$Ph, H; R^2 = alkyl

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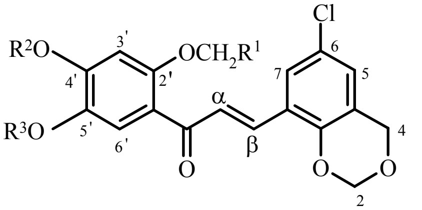
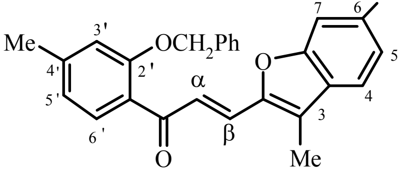
Significant paramagnetic shifts are observed in the ^{1}H NMR spectra of their solutions containing Eu(fod)$_3$ [4, 10, 11]. Unusual here was the more active interaction of this LSR with the 2'-benzyloxy derivatives compared with the corresponding phenols (R^1 = H), although the steric hindrances to complexation at the carbonyl group (the most effective coordination center of the carbonyl of chalcones) are increased during 2'-alkylation. The observed lanthanide-induced shifts (LIS) indicate a specific direction of coordination; the LSR reacts to a significant degree at the oxygen atom of the 2'-OCH$_2$Ph group, which usually has a small capacity for coordination. Since the participation of the ether oxygen atom in complexation with the LSR has not in the course of time obtained a rational explanation, it was studied in greater detail in the present work; the reaction of the analogs of chalcones **2-4** (Table 1) with such lanthanide shift reagents as Eu(fod)$_3$ and Yb(fod)$_3$ was investigated.



2a–c



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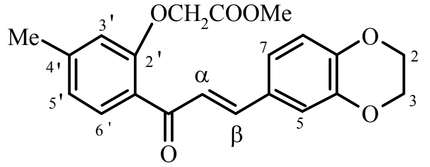

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2 a R^1 = Ph, R^2 = Cl, R^3 = H; **b** R^1 = Ph, R^2 = F, R^3 = H;
c R^1 = OMe, R^2 = H, R^3 = OCH$_2$OMe

During the coordination of Eu(fod)$_3$ with compounds **2c**, **3**, and **4** the previously described effect was observed; it takes place to a significant degree at the oxygen atom of the 2'-OCH$_2$R^1 fragment. This is demonstrated by the larger lanthanide-induced shifts of the signal for the protons of its CH$_2$ group compared with the LIS of the signals for the olefinic protons and the 6'-H proton in the ArCO fragment of the molecule (see Table 1). The presence of the halogen atom at position 5' (compounds **2a**,**b**) weakens the coordination between the ether oxygen atom and the LSR, which increases substantially with substitution of the substituent R^1 = CH$_2$Ph by the less bulky R^1 = Me (in compound **2c**) or R^1 = CH$_2$COOMe (in compound **4**). For example, in the case of compound **2c** the signal for the protons of the 2'-OCH$_2$ group has a lanthanide-induced shift of 7.8 ppm, whereas the signals of the olefinic protons are shifted by only 3.0 ppm.

The reaction of compounds **2-4** with the LSR Yb(fod)$_3$ takes place in a different way. In this case the largest lanthanide-induced shifts are observed for the signal of the 6'-H proton of the ArCO fragment and the signals of the olefinic protons, whereas the shifts of the signals for the protons of the 2'-OCH$_2$ group are significantly smaller. This indicates preferred coordination of the LSR at the carbonyl group of the chalcone. Such a conclusion is confirmed by calculations of the structure of the LSR–substrate adducts on the assumption that they are purely dipolar in nature and that there is only one coordination center, i.e., the oxygen atom of the carbonyl group.

The McConnel–Robertson equation:

$$\Delta_i^{\text{expt}} = K_i (3 \cos^2 \theta_i - 1) / r_i^3 ,$$

where Δ_i^{expt} is the experimental LIS for nucleus *i* and θ_i and r_i are the polar coordinates of the nucleus in the adduct, is widely used to calculate the structure of the adducts.

The method proposed in [12] is based on the fact the constant K is the same for all magnetic nuclei of a given type. In this case the calculation amounts to a search for a point close to the coordination center where the equation presented above is fulfilled in the best way. We obtained the degree of spread of the calculated K_i values from the average K_{av} in the form of the standard deviation σ, where:

$$\sigma^2 = [\sum_{i=1}^{n} (K_i - K_{av})] / (n - 1),$$

where *n* is the number of magnetic nuclei used in the calculation.

Thus, if three-dimensional coordinates are placed along the two coordinate axes while the standard deviation is placed along the third axis, we obtain a three-dimensional diagram of the values of the standard deviation at each point of space.

For the adducts of $Yb(fod)_3$ with the chalcones **2-4** it was found that the Yb atom in the adduct lies at a distance of 2.5-2.6 Å from the carbonyl oxygen atom on a continuation of the C=O bond, while the calculated lanthanide-induced shifts agree well with the experimental values (Table 1). The results of one such calculation for the adduct of $Yb(fod)_3$ with compound **4** without allowance for the LIS of the signals for the protons of the heterocyclic fragment are shown in Fig. 1 as an example. The coordinates of the atoms in the molecule were determined by minimizing its energy by molecular mechanics. In the figure the planar ArCOCH=CH fragment lies in the *XY* plane, the C=O bond is directed parallel to the *X* axis, and the carbonyl oxygen atom is at point (0, 0). The standard deviation lies along the *Z* axis. In accordance with [12] the minimum corresponds to a point in space for which with localization of the Yb ion at this point there is a better correlation between the calculated and experimental values. This indicates that the calculation agrees with the selected model of complexation, i.e., that coordination of the LSR takes place exclusively at the carbonyl oxygen atom.

Attempts to conduct analogous calculations for the europium adducts of compounds **2-4** were unsuccessful. The observed LIS cannot be interpreted in terms of the existence of the molecule in only one conformation with coordination of the LSR at one coordination center (the carbonyl or ether oxygen atom). We tried to calculate the LIS for these adducts on the assumption that the experimental lanthanide-induced shifts (Δ_i^{expt}) represent the sum of LIS taken with different weight contributions (*n*) due to coordination of the LSR at the carbonyl group of two conformers with respect to bond *a*. In one of them the oxygen atom of the substituent 2'-OCH_2R^1 is at the shortest distance to the carbonyl group (the *s-cis* conformer), while in the other it is at the longest distance from it (the *s-trans* conformer):

$$\Delta_i^{\text{expt}} = n\Delta_{i\,cis} + (1 - n)\Delta_{i\,trans}$$

It was found that even the given approximation does not lead to satisfactory correlation of the calculated and experimental LIS. A third possible approach was based on the idea that the molecule exists in the indicated conformations with a different coordination of the LSR in each of them. It is probably such a situation that is realized in practise. For this model of complexation, however, the search for the minimum of the standard deviation must be made for seven unknowns (the three coordinates of the lanthanide in the two adducts and their ratio), which requires the use of too large an amount of independent LIS in the calculations.

TABLE 1. The ^{1}H NMR Spectra of the Investigated Compounds

Version of spectrum	LIS (in CDCl$_3$), δ, ppm											
	ArCO					–COCH=CH–		Het				
	2'-CH$_2$	3'-H	4'-H or 4'-Me	5'-H	6'-H	α-H	β-H	2,2-H$_2$ or 3-Me	3,3-H$_2$ or 4,4-H$_2$	5-H	6-CH$_3$ or 8-H	7-H
2a+Eu(fod)$_3$	3.1	2.5	1.5	—	3.8	2.9	3.5	1.1	1.1	0.3	—	0.5
2a+Yb(fod)$_3$	2.4 {2.3}	3 {2}	3.0 {1.3}	—	10.1 {10.1}	8.4 {6.0}	10.8 {10.2)	1.4 {-2.47} (1.65)	1.4 {-0.39} (0.68)	0.5 {0.26}	—	1.4 {2.69} (-0.81)
2b+Eu(fod)$_3$	3.4	2.7	1.8	—	5.1	3.5	4.4	1.0	1.0	0.3	—	0.5
2b+Yb(fod)$_3$	2.4 {2.6}	3.0 {2.3}	3.0 {1.4}	—	11.3 {11.3}	8.8 {6.6}	11.4 {11.4}	1.1 {-2.77} (1.85)	1.1 {-0.44} (0.75)	0.5 {0.3}	—	1.0 {3.0} (-0.91)
2c+Eu(fod)$_3$	7.8	4.0	0.3	1.1	5.0	3.0	2.9	0.1	0.4	0.4	—	0.3
2c+Yb(fod)$_3$	7.1 {5.0}	6.5 {4.4}	1.6 {1.5}	2.3 {2.0}	21.7 {21.7}	14.6 {12.8}	17.4 {22.0}	0.8 {-5.3} (3.1)	0.8 {-8.4} (1.45)	0.9 {0.6}	—	1.6 {-5.9} (1.7)
3+Eu(fod)$_3$	6.9	3.4	0.9	4.1	6.3	3.3	4.1	0.5	0.2	0.2	0.2	0.2
3+Yb(fod)$_3$	7.1 {6.7}	2.0 {5.7}	1.7 {2.5}	2.0 {2.6}	29.1 {29.1}	19.1 {17.1}	26.1 {29.5}	-2.5 {-2.9}	-2.5 (-2.9)	0.7 (0.7)	1.7 (2.4)	0.7 {0.7}
4+Eu(fod)$_3$	6.8 {6.3}	4.2	0.7	0.9	4.3	2.2	2.2	-0.6-0.5				
4+Yb(fod)$_3$	7.8 {6.3}	6.6 {5.5}	1.4 {2.4}	2.8 {2.4}	27.4 {27.4}	17.3 {16.1}	20.9 {27.7}	0	0	0.2 {-0.7} (2.6)	2.4 {7.1} (-0.8)	0.7 {-1.4} (7.3)

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* The found and calculated lanthanide-induced shifts of the signals for the protons are given. (The calculated lanthanide-induced shifts for the *s-trans* conformers in relation to bonds *a* and *d* are given in braces, and those for the *s-cis* conformers in relation to bond *d* are given in parentheses.)

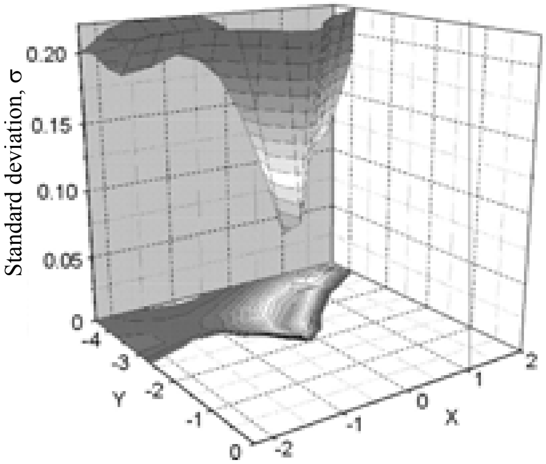

Fig. 1. The results from calculation of the structure of the adduct of $Yb(fod)_3$ with compound **4**. The dependence of the standard deviation σ on the *XY* coordinates is represented by a three-dimensional surface, the minimum of which corresponds to the position of the Yb ion in the adduct. The coordination center is at the origin of the coordinates. For clarity of definition of the coordinates of the minimum a projection of the three-dimensional surface onto the *XY* plane is shown.

The participation of the ether oxygen atom in complexation with $Eu(fod)_3$ is an effect related to the interaction of the LSR with certain other bifunctional compounds described recently [1]. This fits well with the concept of chelation of the bidentate ligand with the LSR, since the observed differences in the coordination of the europium and ytterbium LSR are similar to those described recently for other compounds, such as substituted thiones [13].

It can be concluded on the basis of the observed LIS that the molecules of the investigated compounds in the adducts with various lanthanide shift reagents are in different conformations in relation to bond *a*. In the adducts with $Yb(fod)_3$, in which coordination takes place exclusively at the carbonyl group (without chelation), the *s-trans* conformation is present (see above). Here the 2'-OCH_2R^1 group is distant from the coordination center, and small LIS are observed for its protons. In the adducts with $Eu(fod)_3$, for which a chelate structure is realized, the molecule has the *s-cis* conformation. In this case the 2'-OCH_2R^1 group is close to the lanthanide ion, and significant (in relation to the other signals) LIS are observed for its protons. Thus, the conformation of a molecule of type **1** in relation to bond *a* in the adduct, determined by the LSR method, depends on the shift reagent employed. However, this does not necessarily mean that complexation with the LSR affects the conformation of the molecule; with decrease in temperature there is no significant change in the ratios between the observed LIS, and so there is no redistribution of the weight contributions from the individual conformations of the molecule. Thus, when the spectra are measured at 260 K, there is a small increase in all the LIS, which fits fully into Bleaney's theory of pseudocontact interaction [14]. It can be supposed that when several conformations are realized simultaneously for the molecule and the lifetime of each of them significantly exceeds the time for which the LSR–substrate exists the LSR reacts with the individual conformer almost independently. If coordination of the molecule with the LSR is possible in all its conformations, the resultant LIS will be averaged for all of them, and from their values it is possible in principle to find the conformational composition of the molecule. Such a situation is realized during coordination of the investigated compounds **2**-**4** with $Eu(fod)_3$. If, however, coordination of the molecule with the LSR does not occur in one of the conformations (as in the case of the reaction of compounds **2**-**4** with $Yb(fod)_3$) the resultant LIS are determined only by one or the other conformation in which complexation of the molecule with the LSR is possible. Other conformations are not revealed by means of the LSR, and starting from analysis of the LIS it is possible to show that they are not realized at all. In this case, however, they can be detected by other methods, e.g., by NOE (see, for example, [15]).

The question arises in this connection of the justification for using lanthanide shift reagents in the conformational analysis of compounds of type **1**, since the obtained stereochemistry of the molecule in the adduct cannot correspond to the true conformational composition in the solution. The use of lanthanide shift reagents should probably be restricted to cases where change in the conformation of the molecule does not substantially affect the coordination with the LSR. For the analogs of the chalcones, although it is not possible by means of $Yb(fod)_3$ to determine the conformational composition in relation to bond *a*, it is possible to judge the orientation of the heterocyclic fragment in relation to bond *d*, since with any degree of its rotation about this bond the interaction of the molecule with the LSR takes place in an identical way. Thus, the appreciable diamagnetic shift of the 3-CH_3 group in the adduct of compound **3** with $Yb(fod)_3$ indicates the *s-cis* orientation for the benzofuran fragment in relation to bond *d*, in which this group is closer to the lanthanide, agreeing well with the results from calculation of the LIS. In the other investigated adducts with $Yb(fod)_3$ there is an equilibrium between the two conformations of the heterocyclic fragment, since the values of the experimental LIS lie between those that can be calculated for the *s-trans* and *s-cis* conformers in relation to bond *d*.

EXPERIMENTAL

The ^1H NMR spectra of the investigated compounds were measured on a Bruker WP-100-SY spectrometer (100 MHz). Commercial lanthanide shift reagents were used without further purification. The syntheses of compounds **2-4** and ^1H NMR spectra were described in [16, 17].

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