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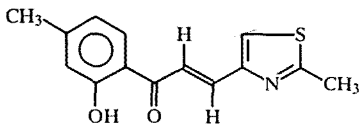
FEATURES OF THE REACTION OF HETEROCYCLIC ANALOGS OF CHALCONE WITH LANTHANIDE SHIFT REAGENTS

A. V. Turov and V. P. Khilya

The PMR spectra of heterocyclic analogs of 2-hydroxychalcone containing thiazole, benzofuran, triazole, imidazole, benzodioxane, or pyridine rings in the presence of lanthanide shift reagents are studied. It is found that the most effective reagent for modifying the spectra of these compounds is Yb(fod)3. The broadening of the spectra of 2-hydroxy chalcones in the presence of lanthanide shift reagents is explained by the dynamic effects of complex formation. An example is given of the determination of the conformation of molecules of 2-hydroxychalcone by the simultaneous use of lanthanide shift reagents and the homonuclear Overhauser effect.

Heterocyclic analogs of the chalcones are important intermediates in the synthesis of corresponding 2- and 3-hetarylchromones. Many of these compounds display significant biological activity [1]. Lanthanide shift reagents have been used successfully in a number of cases to elucidate the structural features of compounds of this type [2-4]. It was possible to simplify the PMR spectra considerably to draw conclusions about the structure of the compound from the values of the induced shifts. However, in cases where there was a hydroxyl group in the 2-position of the benzene ring of heterocyclic analogs of the chalcones, the action of the lanthanide shift reagents often led to an extreme broadening of the signals in the PMR spectra with small shifts of the peaks. Structural information cannot, as a rule, be extracted from such spectra, therefore these chalcones have hardly been studied at all by this method.

We have attempted a more detailed study of the action of various lanthanide shift reagents on heterocyclic, chalcone analogs I-VII and tried to optimize the experimental procedure with them in order to ascertain in what cases the use of lanthanide shift reagents can prove successful.



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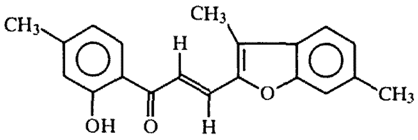

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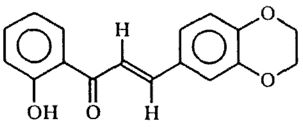

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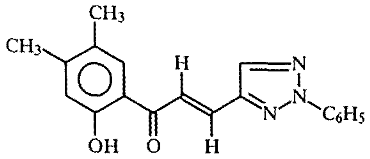

IV

Taras Shevchenko Kiev University, Kiev 252017. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 457-463, April, 1994. Original article submitted March 5, 1994.

TABLE 1. Specific Values of Lanthanide Induced Shifts of Proton Signals in the Chalcones Studies*

Compound	Lanthanide shift reagent	Solvent	Phenolic protons					Olefinic protons		Heterocyclic ring					
			2-OH	3-H	4-R	5-R	6-R	α-H	β-H	1-R	2-R	3-R	4-H	5-H	6-H
I	Yb(fod)$_3$	C_6D_6	13,2	3,7	CH_3, 0,3	H, 0,3	4,5	7,8	6,4	—	CH_3, 2,0	—	—	0,7	—
I	Yb(fod)$_3$	$CDCl_3$	15,4	3,1	CH_3, 0,4	H, 0,5	3,6	6,2	5,3		CH_3, 1,2	—	—	0,0	—
I	Eu(fod)$_3$	C_6D_6	4,8	1,1	CH_3, 0,1	H, 0,3	0,7	1,7	0,9	—	CH_3, 0,4	—	—	0,5	—
II	Yb(fod)$_3$	C_6D_6	10,1	2,6	OCH_3, 0,9		2,5	3,1	2,2	—	—	CH_3, 0,1	—	—	CH_3, 0,2
III	Yb(fod)$_3$	C_6D_6	6,3	—	—			3,1	1,7	—	CH_2, 0,1	CH_2, 0,1	—	—	—
IV	Yb(fod)$_3$	C_6D_6	9,9	2,8	CH_3, 0,6	CH_3, 0,4		2,7	2,1	—	—	—	—	0,3	—
V	Eu(fod)$_3$	$CDCl_3$	2,9	0,3	H, 0	H, -0,4	-0,3	5,2	4,4	CH_3, 2,2	—	H, 6,2	—	—	—
VI	Eu(fod)$_3$	$CDCl_3$	11,6*[2]	2,2	OCH_3, 0,8	H, 2,2	11,6	13,2	9,6	—	CH_2,0,2	CH_2, 0,2	—	1,5	1,4*[3]
VII	Eu(fod)$_3$	C_6D_6	1,8	0,3	H, 0,3	—	0,8	6,5	7,9	—	H, 35,7	—	12,9	13,4	42,7

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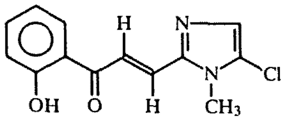
*A dash in the table means that there is no magnetic nucleus in the corresponding substituent;

*[2] Induced shift in the signal of an aromatic proton and not of a hydroxyl, as in the other compounds;

*[3] 7-H proton signal.



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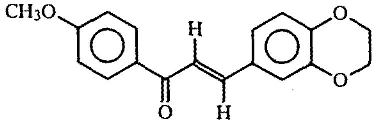

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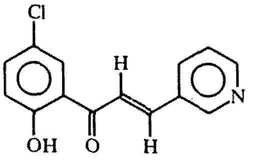


VII

The values found for the lanthanide induced shifts are shown in Table 1. We traced the effect of different lanthanide shift reagents on the PMR spectra of 2-hydroxychalcones in the case of 2-methyl-4-thiazolyl derivative I. Such a widely used reagent as Eu(fod)$_3$ turned out to induce extremely small shifts with a considerable broadening of the PMR lines. The halfwidths of separate lines exceeded 20 Hz in this case. Similar results were obtained with its optically active analog, heptafluorobutyloxymethylenecamphoratoeuropium, Eu(HFBC)$_3$. The sole reagent giving induced shifts of appreciable magnitude with relatively small line broadening proved to be the yttrium reagent, Yb(fod)$_3$. In this case, unlike the experiments with other substrates which were usually run in deuterochloroform, the best results were obtained in deuterobenzene, where the specific induced shifts (calculated for a reagent:substrate ratio of 1:1) can reach 7-8 ppm while preserving the multiplet structure of the signals right up to a reagent:substrate ratio of 0.2. As can be seen from the data in Table 1, the values of the induced shifts can change quite substantially depending on the heterocyclic fragment in the molecule. So, for compounds II-IV, containing heterocyclic fragments, the heteroatoms of which are not able to coordinate to the lanthanide reagent, the specific induced shifts of the olefinic proton lines are no more than 3 ppm. When coordination is possible not only through the carbonyl oxygen atom, but also through a heterocyclic nitrogen atom, the situation is substantially altered: line broadening of the spectra in the presence of the lanthanide reagents disappears and the values of the induced shifts are increased. This makes it possible to do the experiments with these substrates using europium reagents, Eu(fod)$_3$ in particular, which give significantly less line broadening with rather appreciable induced shifts. This is seen particularly clearly with pyridine-containing substrate VII. Here, the hydroxyl proton is practically unshifted in the presence of the reagent, but the pyridine proton lines are very strongly shifted to weaker fields. The induced shifts reach 42 ppm (see Table 1). This shows that coordination in this case occurs exclusively through the pyridine nitrogen atom. A similar result was obtained with chalcone V, which contains an imidazole nucleus. Here, for the 4-imidazole proton, which is close to the coordination site, the specific shift under the influence of Eu(fod)$_3$ was 6.2 ppm, substantially greater than found for the lines of the protons around the carbonyl oxygen atom.

We have also analyzed the possibility of obtaining information of the molecular structure of chalcones with the aid of a quantitative comparison of the experimental values of the induced shifts with values calculated on the assumption of their pseudocontact nature. In this case, an attempt was made to calculate the structure of the adduct with molecule I by the method described in [5]. We found that the correlation between the calculated and experimental induced shifts is not satisfactory for substrates of this kind. This is probably due to the impossibility of precisely determining the coordination site of the molecule with the lanthanide shift reagents, a datum absolutely necessary for carrying out the calculation. The reason for this is that, strictly speaking, the molecules under consideration contain not one, but two coordination sites located close together — a phenolic hydroxyl and a carbonyl oxygen atom. It is known that a carbonyl group coordinates with lanthanide reagents much more effectively than phenols [6], so one would expect the carbonyl to be the most active coordination site in molecules I-VI. However, the phenol group forms a strong hydrogen bond with the neighboring carbonyl, and the electron donating properties of the latter become similar to those of the phenols. Thus, for chalcones containing a 2-hydroxyl group, coordination with shift reagents can occur with about the same effectiveness through the phenolic and the carbonyl oxygen atoms. The observable induced shifts under conditions of rapid or intermediate exchange, on the NMR time scale, are averaged for coordination of the reagents at the two possible coordination sites. In this case, the direction of the effective principal magnetic axis of the adduct is undefined because it is unknown to what extent each of the coordination sites participate in the formation of the adduct with lanthanide shift reagents. Consequently, whichever of the donor atoms we assign as the coordination site, the results are wrong. The proposed scheme for the formation of adducts of the 2-hydroxy-containing chalcones with lanthanide shift reagents is confirmed by the spectra of product VI, which does not contain a hydroxyl group. In this case, the values of the induced shifts prove to be much better than for the 2-hydroxy-containing chalcones, and the lines do not show anomalous broadening.

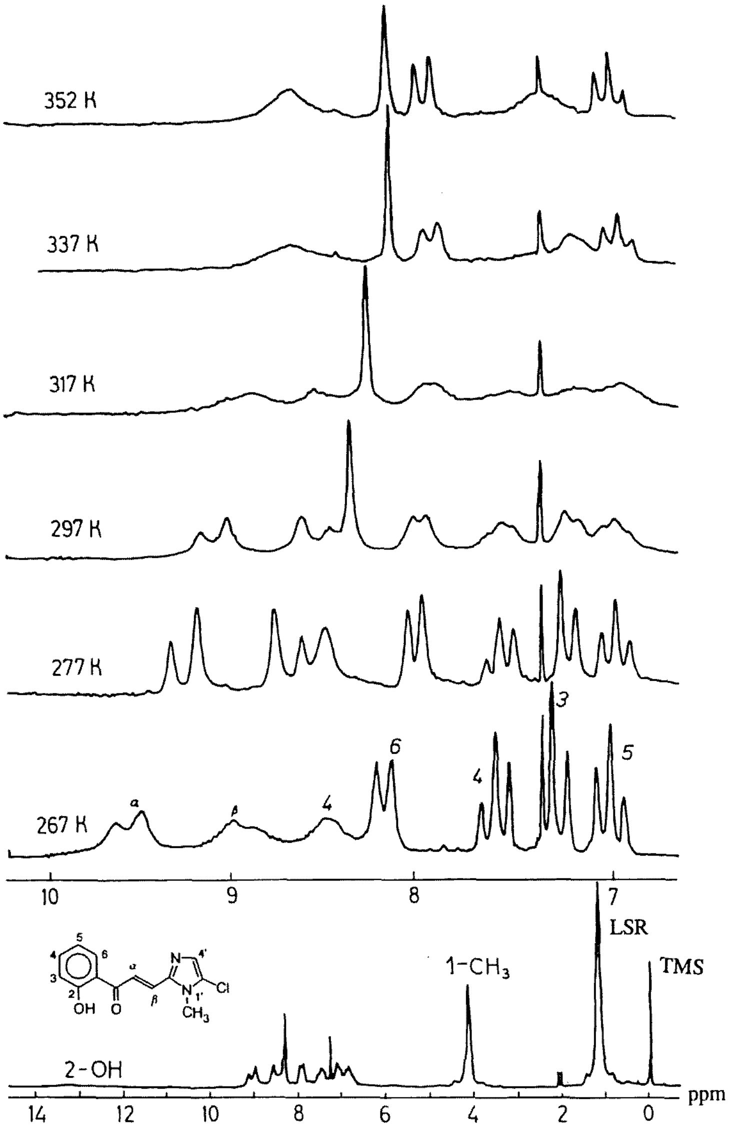
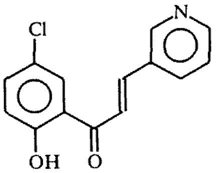


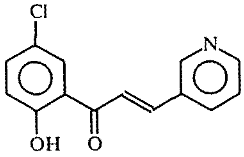
Fig. 1. Temperature dependence of the NMR spectrum of chalcone V in the presence of Eu(fod)$_3$. Ratio of lanthanide shift reagent to substrate is 0.18.

The reason for the considerable broadening of the NMR lines of 2-hydroxy-containing chalcones in the presence of lanthanide reagents is a matter of interest. It was hypothesized earlier [7] that such broadening is contact in nature. However, it remains unclear in this case why broad lines are not characteristic of the spectra of other electron donor molecules which form even more stable adducts with such reagents. We consider the reason for the broadening to be the presence in the molecules being considered of nearby sites for coordination with the lanthanide compounds that have slightly different energies of complex formation. Here, the line broadening in products I-IV in the presence of lanthanide reagents is due to dynamic effects of complex formation at coordination sites that are close together. An indication of this is the anomalous change in the spectra in the presence of lanthanide reagents when the sample temperature is changed. For other substrates, an increase in temperature usually leads to a decrease in the values of the induced shifts and a narrowing of the NMR lines [8], and the opposite effects occur on cooling. In the case of samples I-IV, heating the sample leads, in addition to decreasing the induced shifts, to a broadening of the lines, and cooling leads to an increase in the induced shifts and to some narrowing of the lines. The observed effects can be explained if it is assumed that at room temperature complex formation of lanthanide reagents with a 2-hydroxychalcone molecule takes place at a rate that is intermediate on the NMR time scale. In this case, cooling the sample can lead to the predominance of coordination of the reagent at one of the coordination sites and, correspondingly, to a decrease in the dynamic broadening of the lines.

The temperature dependence of the induced shifts for the adduct of imidazole-containing chalcone V with Eu(fod)$_3$ proved extremely interesting (see Fig. 1). At room temperature (297 K) the spectrum consists of a set of broad lines with peak halfwidths of about 15 Hz. When the temperature is lowered to 277 K, the lines are narrowed, and one can see in the spectrum the individual lines of all the protons on molecule V with the multiplet structure clearly expressed. When the temperature is lowered further, the lines located close to the coordination center (the nitrogen atom of the imidazole nucleus) are broadened. When the temperature is increased to more than 317 K, the lines of the olefinic protons and the 3-H and 4-H protons merge into broad lines. A marked narrowing of the other lines is noted. We explain the effects observed by a change in the rate of rotation about the bond between the imidazole nucleus and the olefinic portion of the molecule. At temperatures a little above room temperature, there is a rather rapid transition between the two planar conformations, but at lower temperatures the compound exists primarily in the one of them that is energetically more favorable. That such effects were not found for the other chalcones, we ascribe to the fact that for them the region where the rates of exchange between conformations are intermediate on the NMR time scale lies at temperatures not accessible in the solvent used.

One of the reasons for the effectiveness of the use of lanthanide shift reagents to determine the structures of electron donor molecules is the possibility of using the homonuclear Overhauser effect for spectra in the presence of lanthanide reagents. The presence of induced shifts affords a considerable increase in the separation between the peaks in the spectra, and thus allows one to conduct Overhauser effect experiments under these conditions when this cannot be done successfully in the initial spectra of the substrates. We carried out corresponding experiments for the adduct of Eu(fod)$_3$ with pyridine-containing chalcone VII with a reagent:substrate ratio of 0.17. Spectra obtained with supplemental irradiation of the olefinic proton lines proved particularly informative. Thus, we found that with the {α-H}, the intensity of the line of 6-H proton in the benzene ring is increased by 28%, and that of the 4-H line of the pyridine nucleus by 13%. In the {β-H} experiment, the lines of these same protons increased by 4% and 11%, respectively. From the results obtained the conclusion can be drawn that the molecule has four planar conformations.


ZEEE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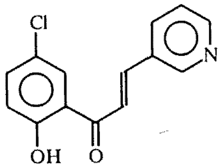
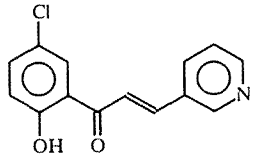

ZEEZ


ZZEZ

The content of conformations ZZEE and ZZEZ in this case is 3-4 times greater than of the other two.

Attempts to observe the Overhauser effect in the spectra of chalcones I-IV in the presence of Yb(fod)$_3$ were not successful even for lines of closely neighboring protons with considerable differences in chemical shifts. Most probably, this is because of the greater effect of the paramagnetism of the ytterbium on the relaxation of the magnetic nuclei of the substrate molecules compared with the corresponding adducts with Eu(fod)$_3$.

Thus, application of lanthanide shift reagents to modify the NMR spectra of 2-hydroxychalcones proves most successful in those cases where the studied molecule contains, apart from the ketonic carbonyl, another, distant, site for coordination with such reagents. When such a site is absent, appreciable shifts of the NMR lines can be successfully obtained with use of Yb(fod)$_3$. However, quantitative treatment of the resultant values of the induced shifts must be carried out with caution.

EXPERIMENTAL

NMR spectra were measured on a WP100-SY spectrometer with an operating frequency of 100 MHz. Commercial lanthanide shift reagents were used in the work without further treatment. Synthesis of the chalcones studied and their spectral characteristics are described in [2, 4, 9].

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