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INVESTIGATION OF THE SPATIAL STRUCTURE OF THE SESQUITERPENE LACTONE HANPHYLLIN BY ^{1}H NMR SPECTROSCOPY USING THE SHIFT REAGENT Eu(FOD)$_3$

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The spatial structure of the sesquiterpene lactone hanphyllin has been investigated by ^{1}H NMR spectroscopy using the shift reagent Eu(FOD)$_3$. Its use enabled us to determine constants and to identify some signals important for confirming the structure and also to establish important characteristics of the conformation of hanphyllin in solution.

The sesquiterpene hanphyllin was isolated in 1976 from the leaves of *Handelia trichophylla* [1]. The structure of hanphyllin was established by spectral and other physicochemical methods — in particular, by NMR spectroscopy [2]. The absolute configuration of the crystalline phase was established by the x-ray structural method [3]. Nevertheless, it was of interest to study the configuration of the molecule in the liquid phase. The methods of NMR spectroscopy are the most promising for this purpose. However, because of the complex overlapping of the signals, the initial spectrum of hanphyllin does not permit the use either of double-resonance methods (nuclear Overhauser effect, recording of INDOR spectra, etc.) or the sequential analysis of the spin–spin coupling constants. In [2], the use of a shift reagent made it possible to to identify the most important signals for confirming the structure and revealing only some spin–spin coupling constants.

We have made an attempt to investigate the systematic use of the shift-reagent procedure in NMR spectroscopy together with computer modeling for a more detailed investigation of the spatial structure of hanphyllin in solution.

As is known, when the spectra of various organic compounds are recorded in the presence of shift reagents a displacement of the lines of the spectra takes place which depends on the concentrations of the molecule under investigation and of the shift reagent and on the distances of the protons to the coordination center, i.e., to the Eu^{3+} ion:

$$\delta = K\frac{3\cos^2\theta_i - 1}{r^3_i}, \quad (1)$$

where K is a constant that depends on $[C_{\mathrm{Eu}}]/[C_X]$;

θ_i is the angle between the axis connecting the paramagnetic center and the atom of the functional group [sic]; and r_i is the distance between the nucleus under consideration and the paramagnetic center.

We have used this relationship for analyzing the spatial structure of the hanphyllin-Eu(FOD)$_3$ complex. A series of spectra were taken in which the concentration of the shift reagent rose and, correspondingly, the spectral lines underwent shifts proportional to the concentration of the shift reagent up to saturation of complex-formation at the point $C_{\mathrm{Eu}}/C_x = 0.8$. From the results of the experiment we plotted a graph of the dependence of the chemical shifts of the protons (δ, ppm) on the ratio of the concentrations of shift reagent and hanphyllin (Fig. 2).

It can be seen from the graphs that up to a ratio $C_{\mathrm{Eu}}/C_x = 0.8$ the relationship is linear, and then, with a further rise in the concentration of the shift reagent, saturation sets in. From the fact that the shift of the signal of the proton present in the geminal position to the —OH group has the highest rate of change it may be concluded that the coordination bonding of

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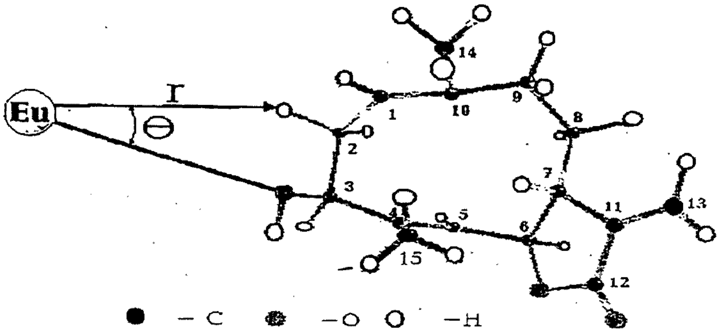

Fig. 1. Spatial structure of the Eu(FOD)$_3$-hanphyllin complex.

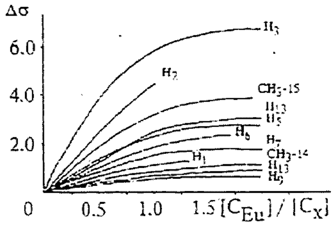

Fig. 2. Graph of the dependence of $\Delta\sigma$ on C_{Eu}/C_X.

the reagent takes place at the —OH group, which agrees with the literature, even though there is a carbonyl group with fairly close activity in hanphyllin. The behavior of the curve of the signal of the H-13 proton shows that, as the coordination of the reagent with the hydroxy group reaches saturation, coordination of the shift reagent with the —C=O group, as well, begins.

An obvious initial hypothesis on the spatial structure of hanphyllin in solution was the crystal structure and the structure obtained from it by optimization using the method of molecular mechanics (MM) for the gas phase. In order to correlate the results of NMR spectroscopy, the x-ray structural investigation, and the MM calculations, we have written a CONRAY program. This program, which was based on a hypothetical structure of the molecule, best selects the position of the coordinating center, measures distances from the coodination center to protons, and calculates the correlation coefficient for these distances with the NMR results in accordance with formula (1).

A simplified block scheme of the program is given in Fig. 3, which shows that the program includes initial information on the coordinates of the atoms of the conformation under investigation, after which the initial coordinates of the Eu atom are calculated. In the next block the Eu coordinates are optimized in agreement with the experimental results and the coefficient of the correlation of the hypothetical structure with the experimental results is calculated. The output of the results of the calculation completes the program.

The program yielded the final characteristics given in Tables 1 and 2.

This investigation has permitted the identification of important signals that could not have been revealed by other methods because of complex overlapping. It has been ascertained that the coordination of Eu(FOD)$_3$ takes place almost completely at the —OH group, since this direction showed a high correlation coefficient, $R = 0.95$. However, as can be seen from the graphs of the relationship $\Delta\delta = f(C_{Eu}/C_x)$, the different behavior of the exomethylene protons shows slight complex-formation at the C=O group, as well.

The C—O—Eu angle has a value of from 118° to 122°, which agrees with the literature [5]. This angle is very important: it shows the position of Eu relative to the plane of hanphyllin. The distance between Eu and O is 3.20 Å, which agrees with results obtained previously by other workers [5]. In spite of the clear existence of conformational transitions (according to the NMR spectrum, the protons at C-2 are equivalent), the structure of the skeleton of the hanphyllin molecule is, on average, close to the crystallographic and calculated structures.

Thus, as a result of the investigation performed we have established the geometry of the complex of Eu(FOD)$_3$ with hanphyllin in solution. The high correlation coefficient has enabled us to state that the conformation of hanphyllin in solution is very close to the crystallographic structure.

TABLE 1. Characteristics of the Angles θ_i and Distances r_i of the Europium—Hanphyllin Complex

Number of the conformation, number of the proton	1* RAY		2*OPT	
	r_i, Å	θ_i deg	r_i, Å	θ_i, deg
H_1	7.46	44.2	7.91	44.5
H_2	6.23	48.6	6.41	47.5
		37.7		38.9
H_3	5.07	26.7	5.19	25.8
H_5	6.82	24.1	7.36	25.3
H_7	9.09	29.4	9.69	24.9
H_9	10.1	46.7	10.4	45.8
		43.7		43.4
H_{13}	12.3	22.7	12.8	20.4
H'_{13}	12.7	28.8	12.9	28.1
CH_3-14		43.7		41.6
	9.24	35.4	9.38	45.1
		45.6		31.9
CH_3-15		11.3		23.7
	6.97	17.5	7.04	13.5
		23.1		13.6
H_6	8.97	16.0	9.16	15.7

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*RAY) characteristics of the configuration of the complex for the crystalline phase; OPT) characteristics of the configuration of the complex calculated by the MMP2 method for the gas phase.

TABLE 2. C–O–Eu Angles and Eu–O Distances for Each Conformation

Number	α, C-O-Eu, deg	r, Eu–O, Å	R (correl. coeff.)
^{1}RAY	123.5	3.18	0.95
^{2}OPT	118.8	3.38	0.95

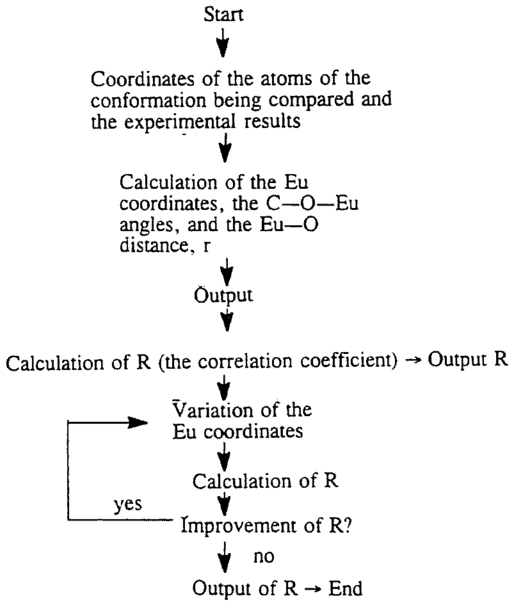

Fig. 3. Simplified block scheme of the CONRAY program.

EXPERIMENTAL

PMR spectra were recorded on a TESLA-BS 567 A NMR spectrometer with a working frequency of 100 MHz. Samples of hanphyllin and of the shift reagent were prepared in the form of solutions with the given concentrations in $CDCl_3$

and were then mixed with one another in the given ratio. HMDS (hexamethyldisiloxane) was used as internal standard. As the shift reagent we used tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane-4,6-dionatoEu(III), Eu(FOD)$_3$, the coordination center in which is Eu^{3+}. The shift reagent was first purified by vacuum distillation at 200°C. Calculations by the MM method were performed by Allinger's MMP2 program [6].

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