USE OF THE PARAMAGNETIC-SHIFT AGENT $Eu(DPM)_3$ TO STUDY THE PMR SPECTRA AND STEREOCHEMISTRY OF ARNIFOLIN

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At the present time, in the solution of stereochemical problems with the aid of PMR spectra, paramagnetic-shift agents (PSAs), especially the complexes of dipivaloylmethane with lanthanides capable of increasing their coordination number, are being used ever more widely [1, 2]. In invert solvents, with compounds containing functional groups PSAs form complexes through a coordination bond of the lanthanide ion, such as Eu^{3+}, with the unshared pairs of the heteroatoms. Paramagnetic-shift reagents cause large downfield shifts of the signals of the protons, the main contribution being made by the pseudocontact shift.

With a change in the concentration of $Eu(DPM)_3$ in solution, a linear relationship is found between the shift of the signals of the protons and the relative molar concentrations of the $Eu(DPM)_3$ and the substance. The use as a measure of the paramagnetic shift of the magnitude $\Delta_{Eu} = \delta^{n=1}_{Eu(DPM)_3} - \delta_{solvent}$ [where n is the ratio of the molar concentrations of $Eu(DPM)_3$ and substance] has been adopted [3].

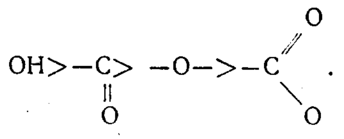
As has been shown previously [1, 4], the magnitude of the paramagnetic shift Δ_{Eu} must vary in inverse proportion to R^3 (where R is the distance between the proton and the Eu^{3+} ion).

The phenomenon of the paramagnetic shift has been studied best for compounds with one functional group [1-3], and less well for bifunctional compounds [5, 6], while there are practically no investigations of this type for polyfunctional substances.

In a study of the influence of PSAs on the PMR spectra of compounds with several heteroatoms, including the compound which we are now considering, the question of the predominant direction of complex formation is important, since this determines the nature of the dependence of the magnitudes of the shifts of the signals on the proton–Eu^{3+} distance.

To answer this question it is necessary to take into account 1) the relative strength of the complexes of monofunctional compounds with the PSAs, which are determined by the nature of the groups [2], 2) the spatial accessibility of the functional groups for the formation of coordination bonds with the $Eu(DPM)_3$, and 3) the effects of the conjugation of various groups with the unsaturated bonds and atoms with the unshared pairs of electrons [5].

Sanders and Williams [2] have shown that in monofunctional oxygen-containing compounds the capacity of the functional groups for associating with PSAs changes in the following sequence:



$$OH > -\underset{\underset{O}{\|}}{C}- > -O- > -C\overset{\nearrow O}{\underset{\searrow O}{}} .$$

Whether such a sequence will be observed in polyfunctional molecules cannot be stated a priori. Thus, from the example of an oxetane derivative containing a sterically hindered hydroxy group it can be seen that this

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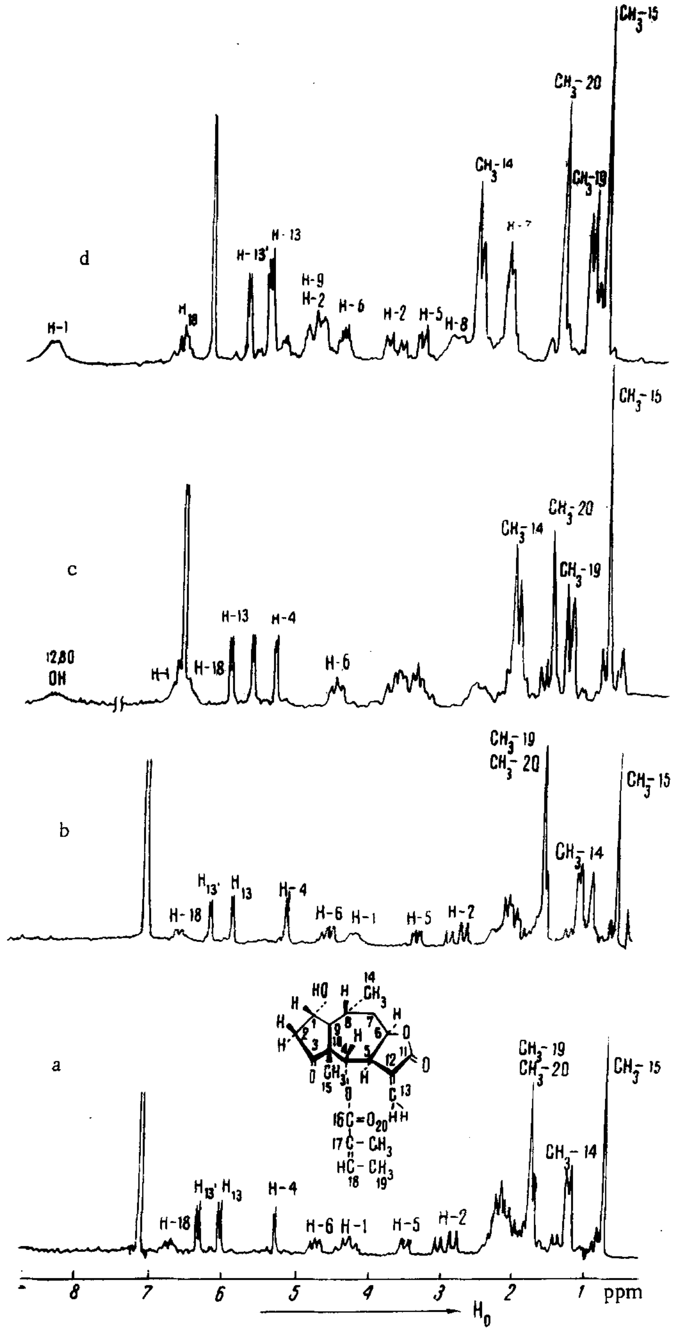

Fig. 1. PMR spectrum of arnifolin (20.5 mg, $0.57 \cdot 10^{-4}$ M, $CDCl_3$) in the presence of various amounts of $Eu(DPM)_3$: a) 0.00 mg; b) 2.1 mg, $0.03 \cdot 10^{-4}$ M; c) 15.2 mg, $0.22 \cdot 10^{-4}$ M; d) 22.7 mg, $0.32 \cdot 10^{-4}$M (frequency 100 MHz, internal standard TMS).

group possesses a smaller associating capacity than an ether oxygen for which there is no steric hindrance [7]. On the basis of the results of a comparison of saturated and unsaturated ethers, it has been shown [5] that the associating capacity of functional groups decreases when these groups are conjugated with one another and with double bonds.

We have used PSAs in an investigation of the stereochemistry of the sesquiterpene lactone arnifolin, which contains six oxygen atoms potentially capable of coordinating with $Eu(DPM)_3$. We have previously reported the results of a chemical study of the stereochemistry of arnifolin [8]. From arnifolin we obtained a derivative with a known structure in which the configurations of a number of substituents were determined. However, the conditions of obtaining this compound did not permit the possibility of the isomerization of the

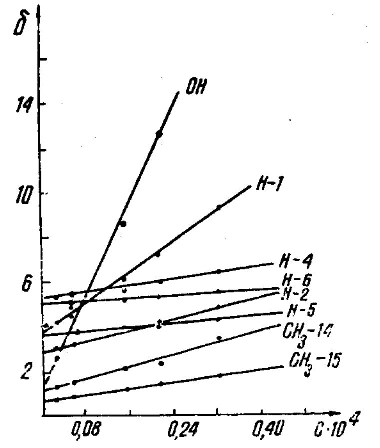

Fig. 2

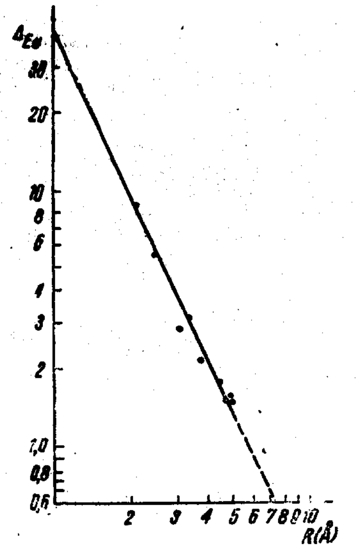

Fig. 3

Fig. 2. Change in the chemical shifts of the protons of arnifolin ($0.57 \cdot 10^{-4}$ M) as a function of the concentration of $Eu(DPM)_3$ [δ is the value of the chemical shifts, ppm, and c the molar concentration of $Eu(DPM)_3$, M].

Fig. 3. Dependence of Δ_{Eu} on R (Å) (where R is the distance between the proton and the oxygen of the hydroxy group) on a logarithmic scale.

substituents in the molecule during the reactions to be excluded. In view of this, it was of interest to study the stereochemistry of arnifolin and, in particular, to determine the position of the OH group relative to the plane of the molecule, which was not found previously.

In a consideration of the structure of arnifolin with the aid of a Dreiding model, it can be seen that of the possible centers of coordination, the OH group is the most accessible, while the carbonyl group at C_3 and the ester carbonyl group are subject to steric hindrance. The effects of conjugation must decrease the associating capacity of the lactone and ester groupings and, consequently, it may be expected that complex formation will take place predominantly at the hydroxy group.

To obtain paramagnetically induced PMR spectra of arnifolin we used tris(dipivaloylmethanato)europium prepared by the method of Eisentraut and Sievers [9]. The PMR spectra were taken on an HA-100D (100 MHz) spectrometer with TMS as internal standard. The concentration of arnifolin in $CDCl_3$ was $0.57 \cdot 10^{-4}$ M, and the concentration of $Eu(DPM)_3$ was varied from 0 to $0.32 \cdot 10^{-4}$ M.*

The PMR spectrum of arnifolin [8] shows the following signals (Fig. 1, a): a singlet at 0.83 ppm (CH_3 at C_{10}), a doublet at 1.32 ppm (methyl at C_8), a quartet at 6.86 ppm (H at C_{18}), and also a doublet at 5.38 ppm, $J = 2$ Hz (H-4), a triplet at 4.84 ppm, $J = 8$ Hz (lactone proton), two quartets at 4.42 ppm (proton at C_1) and at 2.97 ppm (one of the protons at C_2), and two doublets at 6.15 and 6.43 ppm, $J = 3$ Hz (CH_2 group conjugated with a lactone carbonyl). In addition to this, signals are observed at 1.85 ppm (two CH_3 at C_{17} and C_{18}) and 3.55 ppm (proton at C_5; $J_{5,6} = 8$ Hz, $J_{5,4} = 3$ Hz). The signals of the other protons are found in the 1.90-2.40 ppm region. A study of the PMR spectra of arnifolin in this region without a PSA is difficult because of the overlapping of the signals of the protons, which does not enable the necessary parameters of the spectra to be determined.

As an example, Fig. 1 gives the spectra for which the influence of the PSA on the positions of the signals is most considerable. At a molar ratio $n = 0.06$, from the group of signals at 1.90-2.40 ppm in the spectrum of arnifolin (Fig. 1, b) a broad signal of the proton of the OH group separates out at 2.49 ppm, and the other signals undergo practically no displacement. With the addition of $Eu(DPM)_3$ to a molar ratio of the complex and of the initial substance of $n = 0.38$, some changes take place in the spectrum (Fig. 1, c): the

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* Conditions were selected which were close to those described by Demarco et al. [3], whose results we are using.

TABLE 1. Values of Δ_{Eu} and Distances between the OH Group and Various Protons for Some Possible Configurations of the Arnifolin Molecule

Variants*	Protons	H–1	H–9	H–2	H–2	CH_3–14	H–8	H–4	CH_3–15	H–7	H–7
OH CH_3–14 H–8 H–9	Δ_{Eu}	8,75	5,55	5,66	2,93	3,18	2,21	1,77	1,57	1,51	1,51
I − − + −	R (Å)	2,1	2,5	2,5	3,1	3,4	3,8	4,5	4,9	4,7	5,0
II + − + −		2,1	3,2	2,5	3,2	3,4	2,4	4,9	3,8	4,6	4,8
III − + − +		2,1	3,1	2,4	3,2	2,3	2,6	4,3	5,2	4,1	4,6
IV + + − +		2,1	2,4	2,5	3,4	3,7	4,1	4,5	4,05	4,8	5,6
V − − + +		2,1	3,2	2,5	3,2	2,3	3,1	4,5	5,1	4,2	4,3

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* The positions of the groups below and above the plane of the molecule are denoted by the symbols − and +, respectively.

signal of the OH group shifts downfield by a magnitude $\Delta\delta$ 10.40 ppm, and the H-1 signal by $\Delta\delta$ 2.78 ppm. The signals of the protons of the CH_3-19 and the CH_3-20 groups separate. In addition, because of the different shifts of the signals of the protons present at different distances, the spectrum becomes more complicated in the 3.5-5 ppm region, but with the further addition of $Eu(DPM)_3$ ($n = 0.57$) the spectrum again becomes simpler (Fig. 1, d). The signals of a number of protons are shifted downfield by magnitudes of $\Delta\delta$ 2.88 ppm (one of the protons at C_2), 0.95 ppm (at C_7), 1.45 ppm (at C_8), and at 3.65 ppm (at C_9), while the signals of the methyl protons are separated completely. The assignment of the signals at C_8 and C_9 was done by the INDOR method.

The dependence of the chemical shift on the concentration of the complex for a number of protons is shown in Fig. 2. On comparing the concentration curves for arnifolin and for cis-4-butylcyclohexanol [3] it can be seen that the slopes of the curves for the OH group and for the proton at C_1 in the former compound amount to approximately 75% of those in the latter. The difference is apparently due to association of the PSA, but with a different heteroatom of the arnifolin molecule. In agreement with the literature [3], instead of the correlation of the magnitudes of Δ_{Eu} with the distances between the protons and the Eu^{3+} ion we used the more approximate correlation of the magnitudes of Δ_{Eu} with the distances from the protons to the heteroatom taking part in coordination with the $Eu(DPM)_3$.

Table 1 gives the values of Δ_{Eu} for the protons of arnifolin and the distances R (Å) from the proton to the oxygen atom of the hydroxy group measured with the aid of a Dreiding model for four (out of the eight possible) variants of the mutual arrangement of the atoms and functional groups at C_1, C_8, and C_9.

Structures with a cis arrangement of the H-8 and H-9 protons are excluded, since the spin–spin coupling constant measured by the INDOR method of $J_{8,9} = 12$ (for anhydrotetrahydroarnifolin) corresponds to the trans arrangement of H-8 and H-9 (structures I-IV). The selection of the correct configuration from the other four can be made on the basis of the results obtained with the aid of the PSA. The results of a comparison of the values of Δ_{Eu} and the distances between the OH group and the various protons show that the greatest agreement in these magnitudes is obtained for structure I.

The paramagnetic-shift method permits the confirmation for the arnifolin molecule of the trans arrangement of the H-8 and H-9 protons. For structure (V), which is given in the table as an example of a configuration with a cis arrangement of the H-8 and H-9 protons, there is no correspondence between Δ_{Eu} and the proton–hydroxy group distances.

Figure 3 shows the dependence of Δ_{Eu} on the proton–hydroxyl distance in logarithmic coordinates for configuration (I). After the treatment of the experimental results by the method of least squares, the correlation coefficient was 0.92 and the angle of slope 2.1. It can be seen from Fig. 3 that the points corresponding to the protons adjacent to the OH group lie satisfactorily on a straight line $y = Ax + B$ (with $A = -2.1$; $B = 3.7$). At the same time, almost all the points relating to the protons close to other centers of coordination are located above the line, which shows an additional paramagnetic contribution of the $Eu(DPM)_3$ to the shift of the signals of these protons.

A. V. Varlamov assisted in the synthesis of the europium dipivaloylmethanate.

SUMMARY

1. The configuration of the OH group has been determined and the configurations of a number of other protons in the arnifolin molecule have been confirmed by means of the paramagnetically induced PMR spectra.

2. The paramagnetic shifts of a number of protons can be explained satisfactorily if it is assumed that the predominant association of the $Eu(DPM)_3$ is with the hydroxy group.

LITERATURE CITED

1. C. C. Hinckley, J. Amer. Chem. Soc., 91, 5160, No. 18 (1969).
2. J. K. M. Sanders and D. N. Williams, J. Amer. Chem. Soc., 93, 641, No. 3 (1971).
3. P. V. Demarco, T. K. Elzey, R. B. Lewis, and E. Wenkert, J. Amer. Chem. Soc., 92, 5734, No. 19 (1970).
4. N. M. McConnel and R. E. Robertson, J. Chem. Phys., 29, 1361 (1958).
5. H. Hart and G. M. Love, Tetrahedron Lett., No. 7, 625 (1971).
6. C. C. Hinckley, M. R. Klotz, and F. Patil, J. Amer. Chem. Soc., 93, No. 10, 2417 (1971).
7. S. Farid, A. Ameya, and M. Maggio, Chem. Communs. 1285 (1971).
8. R. I. Evstratova, V. I. Sheichenko, K. S. Rybalko, and A. I. Ban'kovskii, Khim.-Farmats. Zh., No. 9, 39 (1969); Khim. Prirodn. Soedin., 270 (1971).
9. K. J. Eisentraut and R. E. Sievers, J. Amer. Chem. Soc., 87, 5254 (1965).