NMR STUDY OF THIA DERIVATIVES OF ADAMANTANE WITH SHIFT REAGENTS

M. HÁJEK, J. JANKŮ, J. BURKHARD and L. VODIČKA
Laboratory of Synthetic Fuels,
Institute of Chemical Technology, 166 28 Prague 6

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2-Thiaadamantane (*I*), 2,2-dioxy-2-thiaadamantane (*II*), 2-thiaadamantane-4-one (*III*), 2-thiaadamantan-4,8-dione (*IV*), 2-thiaadamantan-4-ol (*V*), and 2,2-dioxy-2-thiaadamantan-4-ol (*VI*) were studied with shift reagents. To the sulfide sulfur in *I* the shift reagent $Yb(FOD)_3$ coordinates best. The evaluation employing the equation of pseudocontact shift for the compounds *I* and *II* indicates two coordination sites in the direction of the free electron pairs or oxygen atoms. For the compounds *III* and *IV* the correctness of assignment of the protons to the signals is discussed based on the decoupling technique and the solution of the equation of pseudocontact shift. In the case of the compounds *V* and *VI* the configuration of the hydroxy group was determined.

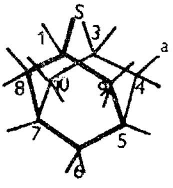
Only little attention has been paid to the study of limit induced shifts for compounds with sulfur-containing functional groups such as thiols (—SH), sulfoxides (—SO), sulfones (—SOO) and sulfides (disulfides)[1-10]. Coordination of a shift reagent to sulfides was expected only to a low extent.[5,7-10] In the case of thiols, the coordination of the shift reagent is lower as compared with alcohols, proportionally to the ratio of basicities of the two types of compounds. For other types of compounds, first of all the possibilities of utilization of the lanthanide shift reagents for conformation and configuration analyses were examined.

In this work we focused our attention on the group of compounds[10-15]: 2-thiaadamantane (*I*), 2,2-dioxy-2-thiaadamantane (*II*), 2-thiaadamantan-4-one (*III*), 2-thiaadamantan-4,8-dione (*IV*), 2-thiaadamantan-4-ol (*V*), and 2,2-dioxy-2-thiaadamantan-4-ol (*VI*). Some of these compounds contain, in addition to sulfidic or sulfonic sulfur, a hydroxy or a keto group. From this aspect we examined the application of the shift reagents $Eu(DPM)_3$ and $Eu(FOD)_3$ (DPM is 2,2,6,6-tetramethyl-3,5-heptanedione, FOD is 7,7,7,6,6,5,5-heptafluoro-2,2-dimethyl-4,6-octanedione) to the determination of the configuration of the hydroxy group in the compounds *V* and *VI*.

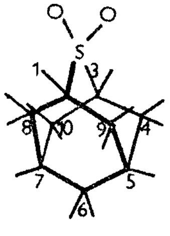
EXPERIMENTAL

For NMR measurements, deuteriochloroform (99·5% deuteration) with 1% tetramethylsilane (Merck, Darmstadt) was used. The solvent was dried with molecular sieve 4 Å prior to use;

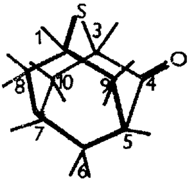
the content of water was lower than 0·01 wt.% (ref.[16]). The compounds *I*—*VI* were sublimated before the measurements.



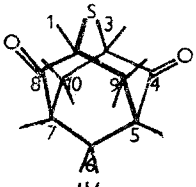
I



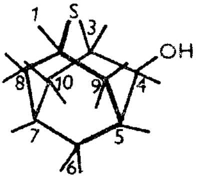
II



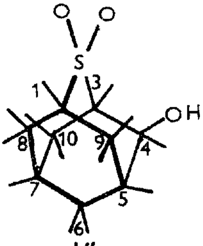
III



IV



V



VI

First the spectra of the compounds without the shift reagents were measured. In most cases the spectra are composed of multiplets. For the identification of the compounds without shift reagents, the following data can be used (p.p.m., δ scale):

I: $H_{1,3}$ —2·83, $H_{4^a,8^a,9^a,10^a}$ —2·5, $H_{4^b,8^b,9^b,10^b}$ —2·16, $H_{7,5}$ —2·16, H_6 —1·86;
II: $H_{1,3}$ —3·04, $H_{4^a,8^a,9^a,10^a}$ —2·54, $H_{4^b,8^b,9^b,10^b}$ —2·09, $H_{3,5}$ —2·01, H_6 —1·81;
III: H_3 —3·18, $H_{1,6^a,5}$ — multiplet 2·85—2·95, H_{8ab} —2·14, H_{other} — multiplet 2·74—2·28
IV: $H_{1,3}$ —3,23, $H_{5,7}$ —2,86, $H_{9^a,10^a}$ —3·10, $H_{9^b,10^b}$ —2·94, H_6 —2·34;
V: multiplet between 3—1·6;
VI: H_4 —2·24, H_{9a} —2·70, H_5 —3·16, H_3 —3·06, other —1·8—2.2.

These values are in a very good agreement with extrapolated ($R_p \rightarrow 0$) values of induced shifts (*vide infra*).

The shift reagents Eu(DPM)$_3$, Pr(DPM)$_3$, Yb(DPM)$_3$ were prepared by the Sievers method[17], the reagents Eu(FOD)$_3$, Yb(FOD)$_3$, Ho(FOD)$_3$, Dy (FOD)$_3$, Pr(FOD)$_3$ were commercial chemicals of Willow Brook Labs., U.S.A. The samples were prepared immediately in the cells by adding the shift reagent to the solution (0·5 ml) of the compound investigated (the substrate) and weighing. From the dependences of the observed chemical shifts $\delta_{i,\text{obs}}$ (for the i-th proton) on the molar ratio of the concentrations of the shift reagent and the substrate (the R_p value), the values of the limit induced shifts (the bound shifts[17]) $\Delta_{i,\text{obs}}$ were obtained by the least squares method (95% probability).

The values of the limit induced shifts were used to solve the equation of the pseudocontact shift[18], $\Delta_i = K(3\cos^2\theta - 1)\, r_i^{-3}$, where θ is the angle between the vector joining the lanthanide atom with the origin (R) and the vector from the lanthanide atom to the i-th proton (r_i), and K is a general constant. The equation was solved by the nonlinear regression method[19,20], employing two basic programs PSEUDO2 and PSEUDO4. With the former program[19] the optimum values of the angles ϕ and ψ, the distance R, and the constant K were sought under the assumption of a single coordination site in the space $+x$, $\pm y$, $\pm z$ (Fig. 1). With the program PSEUDO4 an analogous problem was treated, but two mirror-symmetrical coordination sites were assumed. The lanthanide atom was supposed to lie in the zx plane (Fig. 2).

The correctness of the calculated values was tested by means of the optimization criterion[21] $P = [\sum_{i=1}^{N} (\Delta_{i,obs} - \Delta_{i,cal})^2 / \sum_{i=1}^{N} (\Delta_{i,obs})^2]^{1/2}$, where $\Delta_{i,obs}$ and $\Delta_{j,cal}$ are the observed and calculated values of the limit induced shifts.

The measurements were performed on NMR spectrometers Tesla 467 and Varian XL-100 (temperatures 27 and 37°C, respectively) with the application of CAT. The programs were set up in the language FORTRAN for a computer Tesla 200.

The models of the structures requisite for the calculations were suggested using the Dreiding models (Laboratoriumstechnik, Büchi, Switzerland) or calculations with the KARTSOUR program (according to [22]) employing the common tabulated values of valence distances and bond angles for a six-membered ring (valence distances C—C 0·151 nm, C—H 0·109 nm, C=O 0·121 nm, C—S 0·184 nm; bond angles C—C—C 109·5°, C—S—C 100°, C—C—H 109·5°).

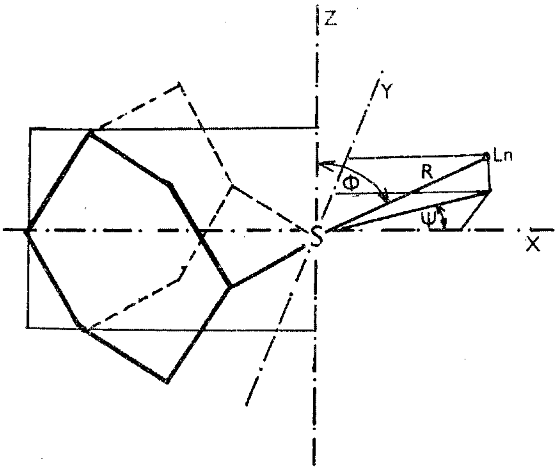


FIG. 1

Option of the Coordinate System and Calculation Parameters for the Solution by means of the Program PSEUDO2

This arrangement was used for the calculations of the limit induced shifts of the compounds *I*, *II*, and *III*.

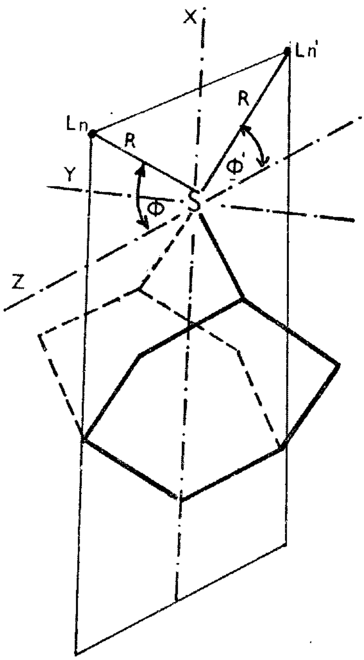


FIG. 2

Option of the Coordinate System and Calculation Parameters for the Solution by means of the Program PSEUDO4

This arrangement was used for the calculations of the limit induced shifts of the compounds *I* and *II*.

RESULTS AND DISCUSSION

Compounds *I* – *VI* can be classified from the aspect of shift reagents as monosubstituted (*I* and *II*) or polysubstituted. With the shift reagent Eu(DPM)$_3$, very low values of limit induced shifts were obtained for the compound *I* (Table I), hence a very low value of the stability constant of the corresponding complex adduct can be inferred. Similarly the shift reagents Eu(FOD)$_3$, Er(DPM)$_3$, Tb(FOD)$_3$, Ho(FOD)$_3$, Pr(DPM)$_3$, and Pr(FOD)$_3$ gave zero or very low values of the limit induced shifts. Only the reagent Yb(FOD)$_3$ gives with 2-thiaadamantane relatively high limit induced shifts (Table I); these shifts were used for the calculations of the position of the lanthanide in the complex adduct. The lanthanide atom was first supposed to lie on the + part of the x-axis (Fig. 1) and the optimum calculated distance S—Yb is then 0·54 nm (optimization criterion $P = 0{\cdot}083$). With the second procedure of calculation two coordination sites were found in the zx plane (Fig. 2) given by the distance S—Yb 0·54 nm and the angle $\Phi = 48°$. This type of coordination seems to be more probable ($P = 0{\cdot}048$). The same calculation carried out for the shift reagent Eu(DPM)$_3$ yields a similar set of parameters of the position of Eu, the value of the optimization criterion is, however, higher. The magnitude of the angle Φ corresponds very well to the position of the free electron pairs, which can participate in the coordination of the shift reagent.

The values of the limit induced shifts for the compound *II* indicate a good coordination of the reagent Eu(DPM)$_3$ (Table I). The calculation performed assuming the

TABLE I

Limit Induced Shifts for the Compounds *I* and *II*

Proton	Compound *I*				Compound *II*		
(i)	$\Delta_{i,obs}{}^{a}$	$\Delta_{i,obs}{}^{b}$	$\Delta_{i,cal}{}^{c}$	$\Delta_{i,cal}{}^{d}$	$\Delta_{i,obs}{}^{a}$	$\Delta_{i,cal}{}^{c}$	$\Delta_{i,cal}{}^{d}$
1,3	1·73	3·71	3·89	3·68	12·01	12·82	12·00
4^a, 8^a, 9^a, 10^a	1·24	3·03	2·76	3·00	9·57	8·51	9·91
4^b, 8^b, 9^b, 10^b	0·80	1·60	1·76	1·69	4·65	5·15	4·49
7, 5	0·76	1·28	1·44	1·36	3·71	4·21	3·11
$6^{a,b}$	0·15	1·19	1·04	0·93	3·45	2·81	2·10
P^e			0·084	0·048		0·10	0·79

[a] With the shift reagent Eu(DPM)$_3$; [b] with the shift reagent Yb(FOD)$_3$; [c] calculated by the PSEUDO2 method, [d] calculated by the PSEUDO4 method, [e] optimization criterion.

lanthanide atom to lie on the *x*-axis (Fig. 1) gives the distance Eu—S 0·33 nm, with the optimization criterion $P = 0{\cdot}1$. For 2,2-dioxy-2-thiaadamantane (*II*) – analogously as for the compound *I* – the assumption of two coordination sites can be applied too (Fig. 2). If the distance sulfur–oxygen in the sulfone group is supposed to be 0·145 nm, then Eu lies in the distance of 0·27 nm from each of the oxygen atoms, and the angle Φ (Fig. 2) in the *xz* plane is 30°. The optimization criterion is here $P = 0{\cdot}079$; it can be assumed that this model of coordination approaches the actual coordination better than that based on the assumption of a single coordination site.

In the case of the compound *III* and the shift reagent $Eu(FOD)_3$ (Table II) the coordination of the reagent to the sulfur atom in the adamantane skeleton can be neglected. This was confirmed by following the induced shifts in an equimolar solution of adamantanone and 2-thiaadamantane. In the range of $R_p \sim 0{\cdot}1-0{\cdot}5$ the value of the limit induced shifts for the protons 1 and 3 of thiaadamantane is 1·4, whereas for the same protons in adamantanone the slope is 16·4. The presence of sulfur in the adamantane skeleton causes a deformation of the whole molecule, and the resultant spectrum with the shift reagent contains separated signals of nonequivalent protons. During the interpretation of the spectrum we had to assign the signal to the parts of the AB system (Fig. 3, signal *c*) which can correspond to the protons 6^a, 9^a, 10^a. From calculations it follows that the coordinates of those protons are very

TABLE II

Limit Induced Shifts for the Compounds *III* and *IV* With the Shift Reagent $Eu(FPD)_3$ Measured at 27°C

Proton (i)	*III*		*IV*
	$\Delta_{i,obs}$	$\Delta_{i,cal}{}^a$	$\Delta_{i,obs}$
1	3·02	2·97	7·16
3	10·68	10·81	7·16
5	10·90	9·15	7·15
6^a	5·67	5·95	4·36
6^b	3·77	3·65	4·36
10^a	4·41	5·85	4·65
10^b	3·77	3·81	4·31
9^a	4·41	5·34	4·65
9^b	2·73	3·61	4·31
8^a	2·73	2·61	—
8^b	2·73	2·61	—
7	2·73	2·95	7·15

[a] Calculated by the PSEUDO2 method, with the resultant value of the optimization criterion $P = 0{\cdot}1388$.

near to each other and so are their distances from the carbon atom $C_{(2)}$ (Table III). Calculations were carried out with the program PSEUDO2 assuming that one molecule of the shift reagent coordinates to the keto group. The orientation was chosen as shown in Fig. 1, with the oxygen atom of the keto group located in the origin of the coordinate system. The calculations were performed for all the possible assignments of the protons 6^a, 9^a, and 10^a. The differences between the optimization criteria are very small (for the position of the lanthanide atom on the prolonged connecting line carbon–oxygen or in the plane of the double bond with the coordination of two molecules of the shift reagent, as well as for the position in the space $+x$, $\pm y$, $\pm z$), so it cannot be unequivocally decided, which proton corresponds to the signal *c* as shown in Fig. 3. The lowest of the optimization criteria corresponds to the assignment of that signal to the proton 10^a. The effective position of the lanthanide is determined by the angles $\Psi = 27°$, $\Phi = 99°$ and the distance $R = 0{\cdot}31$ ($P = 0{\cdot}130$).

The interactions between the signals of the protons 1, 3, 5, 7 and those of the protons 6^a, 10^a, 9^a were investigated by the decoupling technique. The measurements confirmed that the proton 6^a corresponds to the signal *c* (Fig. 3). For this assignment, the calculations performed with the program PSEUDO2 lead to the value of the optimization criterion $P = 0{\cdot}138$ (for data see Table IV). The position of the lanthanide atom is almost the same as that given above ($\Psi = 5°$, $\Phi = 99°$ and $R = 0{\cdot}29$ nm).

The limit induced shifts of the compound *III* transformed to relative values (with respect to the lowest value) can be used for the calculation of the relative limit induced shifts for the diketone *IV*, based on additivity[23]. After the addition of the shift reagent, all five groups of nonequivalent protons can be distinguished (Table II). Assuming the coordination of the reagent to each of the functional groups in the same manner as for the compound *III*, we expected a low value of the optimization

TABLE III

Coordinates of Protons in the Compound *III* Calculated by the KARTSOUR Program[22]
The oxygen atom of the keto group is located in the origin.

Proton	*X*	*Y*	*Z*	Proton	*X*	*Y*	*Z*
1	−4·792	0·148	2·176	10^b	−3·486	−2·273	−1·257
3	−1·310	−2·145	0·000	9^b	−3·876	2·235	1·200
8^a	−5·566	0·881	0·058	5	−1·680	2·177	0·053
10^a	−2·292	−1·321	−2·139	7	−4·578	−0·131	−2·087
9^a	−2·668	1·427	2·199	6^b	−3·749	2·070	−1·306
8^b	−5·566	−0·881	0·058	6^a	−2·454	1·146	−2·067

criterion *P* calculated for the set of data obtained on the basis of additivity, as was the case with 2,6-adamantanedione[23] and 2,6-dioxaadamantane[24]. This assumption, however, did not prove to be right, obviously in consequence of a deformation of the molecular skeleton of the compounds *III* and *IV*. The value of the optimization criterion was $P = 0{\cdot}14$; similar results were obtained with the shift reagent Eu(DPM)$_3$

The hydroxy derivatives *V* and *VI* resemble the compound *III*. The shift reagent coordinates preferably to the hydroxy group. Previous results indicated that the coordination to the sulfide sulfur in *V* can be neglected. Analogously, for low R_p values (up to $\sim 0{\cdot}5$) as applied during the measurements, we can neglect the coordination of the shift reagent to the sulfone group of the compound *VI*. For both compounds we did not know, whether they are present as the *syn* or the *anti* isomer (with respect to the relation between the hydroxy group and the sulfur atom of the adamantane skeleton). As a suitable model compound for a correct assignment of the protons, 2-adamantanol could be used. Table IV presents relative limit induced shifts for some characteristic protons in the molecules of the compounds *V* and *VI* and 2-adamantanol in the presence of Eu(DPM)$_3$. From a comparison the *syn* isomer emerged as the more probable. This was confirmed for the two compounds (Table V) by calculations of the limit induced shifts using the program PSEUDO2. If the set of data is calculated for the *anti* configuration, we obtain values of no physical meaning with inappropriatly high values of the optimization criterion

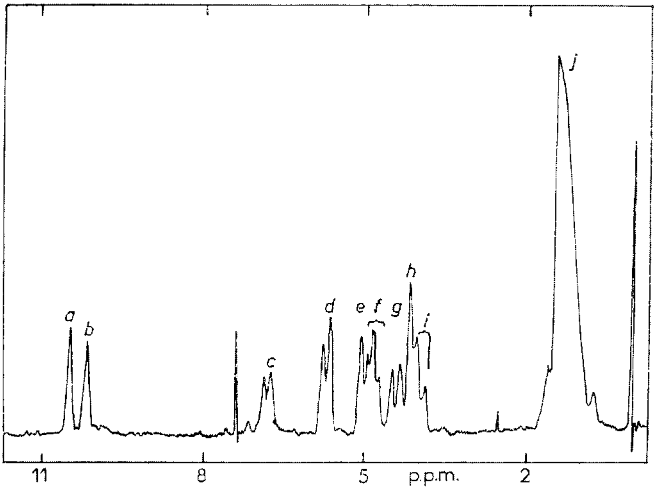


FIG. 3

Spectrum of the Compound *III* with and Addition of the Shift Reagent Eu(DOF)$_3$, $R_p = 1{\cdot}3$ Designation of the protons: *a* 3, *b* 5, *c* 6^a, *d* 9^a, 10^a, *e* 1, *f* 6^b, 10^b, *g* 9^b (?), *h* 7, *i* 8^{ab}, *j* FOD.

TABLE IV

Relative Values of Limit Induced Shifts With Eu(DPM)$_3$ for Some Protons in 2-Adamantanol and the Compounds *V* and *VI*

Assumed coordination to the OH group; numbering as for 2-adamantanol.

Proton (i)	2-Adamantanol $\Delta_{i,rel}$	*V* $\Delta_{i,rel}$	*VI* $\Delta_{i,rel}$
1	2·30	2·53	2·19
2	3·89	4·30	3·73
3	2·30	2·56	2·08
9^a, 4^a	2·39	2·52[a]	2·12[a]
9^b, 4^b	1·07	0·81[a]	0·84[a]
5	1	1	1

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[a] The $C_{(4)}$ carbon atom is replaced by sulfur.

TABLE V

Limit Induced Shifts for the Compounds *V* and *VI* Observed and Calculated for the *syn* Isomers by the PSEUDO2 Method

Shift reagent Eu(FOD)$_3$, temperature 37°C.

Proton	Compound *V*		Compound *VI*	
	$\Delta_{t,obs}$	$\Delta_{i,cal}$	$\Delta_{i,obs}$	$\Delta_{i,cal}$
4	30·18	30·15	25·9	25·06
9^a	17·74	17·41	14·71	15·15
9^b	7·51	8·08	5·86	7·13
5	16·55	16·66	15·22	14·94
3	17·23	16·89	14·44	15·02
1	7·21	7·66	6·93	6·61
10^a	5·36	5·77	5·86	5·51
6^a	4·68	4·42	5·86	4·69
10^b	5·36	5·75	5·75	6·27
6^b	4·41	4·13	5·75	5·36
7	3·97	3·72	4·34	3·94
8^a	4·68	4·78	4·34	4·43
8^b	4·98	5·06	4·34	4·64
P[a]		0·025		0·056

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[a] Optimization criterion.

($P > 0{\cdot}3$). The differences between the calculated and observed values are considerably higher than the experimental error (10%). The most probable positions of the lanthanide atom in the complex adducts of the compounds *V* and *VI* can be depicted as shown in Fig. 4, with the calculated Eu—O distances (oxygen of the hydroxy group) 0·27 and 0·26 nm, and angles $\Psi = 14{\cdot}3^\circ$ and $9{\cdot}6^\circ$ and $\Phi = 155{\cdot}8^\circ$ and $143{\cdot}6^\circ$ in the two compounds, respectively. These data can be well compared with those obtained for 4-hydroxy-2-adamantanone[25].

The study performed with the set of compounds in question shows how vague the structure elucidation with shift reagents can be for some compounds. For those with one functional group, such as *I* and *II*, one can arrive at unique conclusions by solving the equation of pseudocontact shift. In the case of complex molecules, where the skeleton is deformed by the presence of an additional hetero atom (*III*, *IV*), the deformation being, however, relatively small, the assignment carried out employing the optimization criteria can be erroneous. The unreliability of the results should be related probably first of all to that of the determination of the coordinates of the protons in the compounds under study. The actual deformations of the adamantane skeleton may be different from those obtained from the structure calculations, which are based on the data tabulated for a six-membered, ring. With the limit-

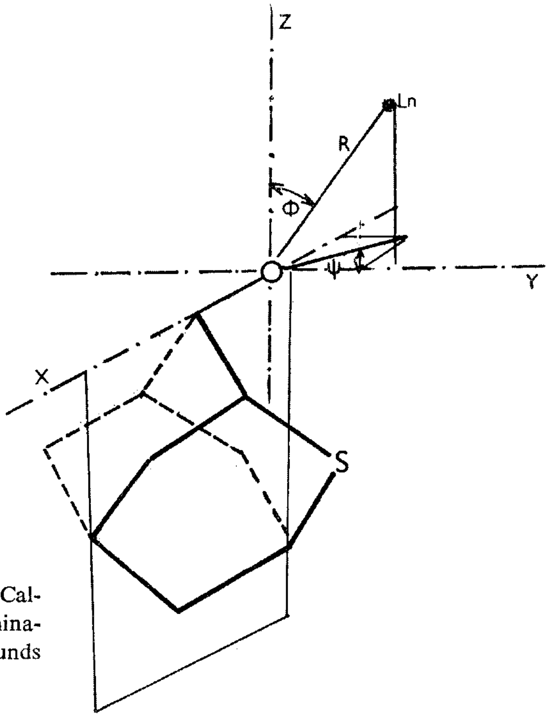

Fig. 4

Option of the Coordinate System and Calculation Parameters for the Determination of the Configuration of the Compounds *V* and *VI* ed possibility of coordination of the shift reagent to the keto group in the plane of the double bond[26], an inaccurate determination of the coordinates can manifest itself by a higher error in the solution of the equation of pseudocontact shift. The compounds *V* and *VI*, where the configurations were studied, give again good results: the differences between the coordinates of the protons in the various configurations are relatively high and a change in the assignment shows up in a large change of the optimization criterion. In addition, the coordination of the reagent is here confined not to the plane of the double bond, but to a cone around the connecting line carbon--oxygen. The effective position of the lanthanide will be in this case closer to the true position in the complex adduct.

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