APPLICATION OF THE RELAXATION REAGENT (2,2,6,6-TETRAMETHYL-3,5-HEPTANEDIONATO)-GADOLINIUM(III) IN ^{1}H-NMR STUDIES OF ADAMANTANE DERIVATIVES

M.HÁJEK, I.MOHYLA, Z.KSANDR and L.VODIČKA

Laboratory of Synthetic Fuels and
Department of Analytical Chemistry,
Prague Institute of Chemical Technology, 166 28 Prague 6

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The application of the relaxation reagent $Gd(DPM)_3$ for structural analysis of organic substances was studied with model substances adamantanone, 2-oxaadamantane, 2,2-dioxy-2-thiaadamantane, 2,6-dioxaadamantane, and 2-thiaadamantane. The technique of simultaneous application of a shift reagent and a relaxation reagent was used. The induced signal widths were corrected for the nonselective effect; for a quantitative evaluation of the data, the theoretical inverse proportionality of the induced signal width to the sixth power of the distance gadolinium–proton measured was employed. From the measurements, the relative distances of the various protons from the coordination centre as well as the absolute distances resulting from calculations based on a modification of the nonlinear regression method were obtained. For the compounds under study, the most probable models of coordination of the relaxation reagent are given.

The wide application of shift reagents in NMR spectroscopy (particularly ^{1}H and ^{13}C) aroused in the last years a new interest in phenomena associated with the presence of a paramagnetic centre in the molecule measured[1]. So we can explain also the initiation of a novel method using the so-called relaxation reagents. This method, apparently competing with the commonly used shift reagent method, has in fact many common features with the latter; for a review see ref.[2].

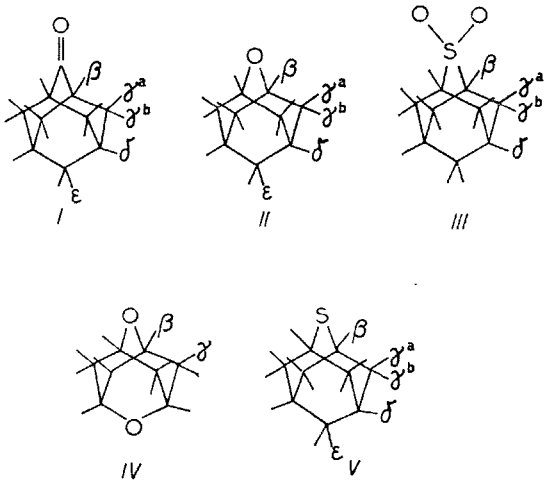
The technique of relaxation reagents was developed by La Mar and Faller[3,4]. It is essentially based on the simultaneous application of a shift reagent and a relaxation reagent in a sample. The addition of the shift reagent – such as $Eu(FOD)_3$ (FOD is 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedione) – to the substance measured leads to high induced shifts in the NMR spectrum and so to the separation of the signals of different nonequivalent groups of nuclei (this is necessary in most cases of ^{1}H-NMR studies; in ^{13}C-NMR, where the span of the chemical shifts is much higher, the addition of the shift reagent need not be required[5]). The addition of a relaxation reagent, such as $Gd(FOD)_3$, brings about a broadening of the signals. The signal width measured prior to the addition of the relaxation reagent is the natural line width, and the difference between the width measured after the addition of the relaxation reagent and the natural width represents the induced line width,

analogous to the induced shift. The broadening is due to the interaction of the paramagnetic central ion with the nuclei measured, which in turn is conditioned by the occurrence of the complex adduct of the substrate with the relaxation reagent in solution. In order to obtain the correct value we must substract the contribution from the nonselective second sphere coordination, which can be best assessed by measuring a similar compound, which, however, does not form an adduct with the relaxation reagent. If the mechanism of relaxation of the measured nuclei by the unpaired electrons of the central ion is the dipole–dipole interaction and if the electron spin g-tensor is isotropic, which holds in the case of Gd^{3+}, then the broadening of the signal (induced width) for the i-th group of nuclei, $\Delta\nu_i$, is inversely proportional to the sixth power of the distance between the paramagnetic centre and the i-th nucleus, r_i:

$$\Delta\nu_i = kr_i^{-6} . \qquad (1)$$

This forms a basis for the utilization of relaxation reagents for structural analysis of organic compounds. In fact, the $\Delta\nu_i$ values cannot be determined with very high an accuracy; the sixth power in Eq. (*1*), however, allows the use of less accurate data too.

In our laboratory we studied the possibilities of application of the relaxation reagent $Gd(DPM)_3$ (DPM is 2,2,6,6-tetramethyl-3,5-heptanedione) with several compounds possessing a rigid structure, belonging to the series of 2-substituted adamantane derivatives, *viz.* adamantanone (*I*), 2-oxaadamantane (*II*), 2,2-dioxy-2-thiaadamantane (*III*), 2,6-dioxaadamantane (*IV*), and 2-thiaadamatane (*V*). A shift reagent of the type $Ln(DPM)_3$ or $Ln(FOD)_3$ (Ln is a lanthanoid) was simultaneously added.



EXPERIMENTAL

The relaxation reagent $Gd(DPM)_3$ and the shift reagents $Ln(DPM)_3$ were prepared according to Eisentraut and Sievers[6], $Ln(FOD)_3$ were commercial chemicals of Willow Brook Labs., Wisconsin, USA.

The compounds *I*—*V* were prepared by standard methods in the Laboratory of Synthetic Fuels[7–10]. The samples were prepared by weighing immediately in NMR tubes, in some cases stock solutions of the components were used. The samples were not degasified prior to measuring, as the relaxational contribution of the oxygen dissolved could be considered negligible[11] and, in addition, it is eliminated during the procedure used.

$CDCl_3$ served as the solvent, tetramethylsilane as the standard. ^{1}H-NMR spectra were measured on spectrometers Tesla BS 467, 60 MHz, and Varian XL-100-15, 100 MHz, at temperatures 23° and 37°C, respectively. The signal widths were measured at half heights. All the signals were singlets save the AB doublets of the γ_a and γ_b protons, for which the remaining multiplet structure was removed by the decoupling technique. Calculations were performed on a computer Tesla 200. The programs GDZPR, GDZPR 1, and GDZPR 2, mentioned in the text, are based on a modification of the nonlinear regression method[12,13]. The interatomic distances were obtained from Dreiding models of Büchi, Laboratoriumstechnik, Switzerland. For the calculations using the programs mentioned, the positions of the protons are characterized by their cartesian coordinates, the origin being identified with the oxygen atom for the compounds *I* and *II* and the sulfur atom for the compounds *III* and *V*. The position of the gadolinium atom is determined by its distance from the origin, *R*, and the angles in the X-Y and Z-*R* planes, ψ and φ, respectively (see Fig. 1 for the compound *II*). When the program GDZPR was used, the coordination of one gadolinium atom in the space $\pm X$, $\pm Y$, $\pm Z$ determined by the angles φ and ψ was assumed, whereas for the programs GDZPR 1 and GDZPR 2 a simultaneous coordination of two gadolinium atoms was supposed to occur, with the two atoms lying in the X-Y (GDZPR 1) or X-Z (GDZPR 2) plane, symmetrically with respect to the X axis. A statistical evaluation was performed with the confidence intervals for a 95% probability.

RESULTS AND DISCUSSION

As mentioned above, a correction for the nonselective effect must be substracted from the experimental induced width; the correction must be estimated. For our series of compounds we used as the correction the value of induced width for the signal of adamantane obtained in a solution with the same concentration of $Gd(DPM)_3$ as used for measuring the derivatives under study. As the uncertainty of the experimental value of the induced width obtained with the instruments used is at least 1 Hz, it is sufficient to estimate the correction with the same accuracy. Our measurements showed that for concentrations of $Gd(DPM)_3$ up to about $3 . 10^{-3}$ mol l^{-1} the correction can be neglected, up to $5 . 10^{-3}$ mol l^{-1} amounts to 1 Hz, and up to $8 . 10^{-3}$ mol l^{-1} makes 2 Hz. During the measurements, several additions of the relaxation reagent were applied to the sample of the substance studied (0·1 – 0·2 mol . l^{-1}) and a shift reagent (0·1 – 0·2 mol l^{-1}). The total concentrations of $Gd(DPM)_3$ lay usually in the region of $0·5 – 5 . 10^{-3}$ mol l^{-1}, which is for the series of compounds the optimum range from the point of view of the accuracy of the signal

width measurements (widths up to about 150 Hz). This implies the consumption of $Gd(DPM)_3$ of the order of tenths of milligram.

In all the systems investigated we found the induced widths to be directly proportional to the concentration of Gd $(DPM)_3$, which can be explained – regarding the span of the concentrations applied – similarly as the well-known linear dependence of the induced shifts on the R_p value for the case of shift reagents (R_p is the ratio of molar concentrations of the shift reagent and the substrate[14]).

For the numerical evaluation of the experimental data, two different methods were used. The first of them is the calculation of the relative distances of the individual protons from the central ion with respect to some basic distance, *e.g.*, that of the nearest protons (β). This method has been successfully used[3,5,11]. For the i-th proton we can write

$$r_i/r_\beta = (\Delta\nu_\beta/\Delta\nu_i)^{1/6}\,, \qquad (2)$$

hence the relative distance can be calculated as the sixth root of the ratio of the corresponding induced widths. The relative distances represent a significant structural information and enable *inter alia* the assignment of signals. An advantage of this calculations is its simplicity. If, however, we want to estimate the accurate position of the gadolinium central ion with respect to the molecule examined, we have to use another method, yielding the actual absolute distances and an image of the molecular geometry; the calculations, however, can be in fact carried out only on a computer.

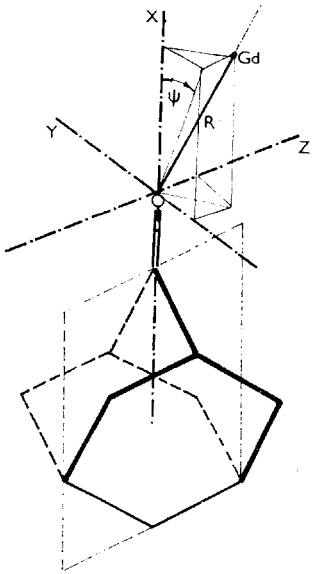


FIG. 1.
Selection of the Coordinate System
The coordinates ψ, φ, and R are along with the constant k the unknown parameters during calculations using the program GDZPR.

By this method we can calculate for an assumed geometry the most probable position of the gadolinium central ion and evaluate the mutual agreement between the experimental and calculated widths. The most probable structure of the compound measured can be then determined by comparing the various structural models. For this purpose we made use of the optimization criterion P_{v_i} defined as $P_{v_i} = [\sum(\Delta v_{i,cal} - \Delta v_{i,obs})^2 / \sum(\Delta v_{i,obs})^2]^{1/2}$, where the subscripts cal and obs refer to the calculated and observed broadenings, respectively.

The calculations were performed by employing programs based on nonlinear regression, as mentioned above. For the program GDZPR (Fig. 1) the position of the gadolinium atom was assumed on the X-axis, which coincides for the compound *I*, for instance, with the prolonged connecting line C=O. The input data were the coordinates of the individual protons in the substrate molecule, the experimental induced widths, the first approximations of the variables (the constant k of Eq. (*1*), angles φ and ψ, and the distance of the gadolinium atom from the origin of the coordinate system), and the information on which of the data should be varied during the optimization procedure and in what way (the variation of the parameters proceeds automatically and is controlled by the minimization procedure[12,13]). During the computation these variables were changed gradually so as to obtain the best fit of the calculated induced widths to the experimental values. The output data contained the resultant values of the variables along with their standard deviations, the calculated values of the induced widths, the coordinates of the most probable position of the gadolinium atom, and the value of the optimization criterion. The programs GDZPR 1 and GDZPR 2 are designed for the calculation of models, where the substrate molecule coordinates simultaneously to two molecules of the relaxation reagent; the computation itself was identical with the previous one, only for the calculation of the induced widths the contributions from two relaxation centres were summed up.

During the analysis of an unknown substance the procedure would be the same; the computation would be applied several times, for the various suggested molecular models (characterized by the coordinates of the individual protons) and the most probable structure would emerge from the comparison of the values of the optimization criterion. This procedure seems to be rather time-consuming (there are different possibilities of signal assignment *etc.*); as a matter of fact, it would be practically used to verify structural information already obtained (found, *e.g.*, by the shift reagent method).

In order to test the possible effect of the shift reagent, we carried out experiments with shift reagents containing all the lanthanoid central ions, which come into consideration from the practical point of view (Pr, Eu, Tb, Dy, Ho Yb), and the ligands DPM and in most cases also FOD. As supposed, neither the central ion nor the ligand of the shift reagent has an appreciable effect on the results of measurements with relaxation reagents. We considered therefore all the measurements as equivalent

for data processing and did not allow for the shift reagent used for inducing the shifts in the NMR spectrum of the substrate prior to adding the relaxation reagent. Yet, $Yb(FOD)_3$ and $Eu(FOD)_3$ appeared to be the most suitable reagents and most of the measurements were carried out with them; in the case of the other reagents the shifting capacity is either lower, so that a sufficient separation of the signals – which is even more important for the determination of the signal widths than for the measurement of induced shifts – cannot be achieved (or it would require a too high R_p value), or, on the contrary, the shifting capacity of the reagent is too high. In the latter case, the high induced shifts are accompanied by a high broadening of the signals, and further broadening by the relaxation reagent cannot be reliably determined.

In the following paragraphs we give account of the results of measurements for the compounds *I* – *V*. For each of them we used (if possible) several shift reagents and for each of the reagents we carried out experiments with several concentrations of the relaxation reagent $Gd(DPM)_3$. We report the average results of measurements at both 60 and 100 MHz and the results of calculations of the relative distances as well as the absolute distances obtained by means of the three programs. The distances Gd^{3+}-functional group used during calculations according to the relation (*2*) were chosen based on a comparative calculation of the lanthanoid position with the use of shift reagents.

TABLE I

Relative Distance of Protons, r_i/r_β, Calculated According to Eq. (*2*)

Compound		Relative distances of the protons			
		γ^a	γ^b	δ	ε
I	*a*	1·20 ± 0·02	1 34 ± 0·03	1·59 ± 0·07	1·66 ± 0·06
	b	1·19 ± 0·04	1·43 ± 0·06	1·66 ± 0·14	1·71 ± 0·09
	c	1·10	1·34	1·48	1·63
II	*a*	1·30 ± 0·13	1·54 ± 0·05	1·87 ± 0·60	1·90 ± 0·38
	b	1·26 ± 0·14	1·43 ± 0·24	1·50 ± 0·30	1·54 ± 0·46
	c	1·31	1·64	1·83	2·00
III	*a*	0·97 ± 0·02	1·31 ± 0·03	1·47 ± 0·05	1·56 ± 0·07
	b	0·97 ± 0·06	1·30 ± 0·02	1·45 ± 0·06	1·55 ± 0·18
	c	0·88	1·22	1·28	1·51
IV	*a*	1·17 ± 0·07	—	—	—
	b	—	—	—	—
	c	1·22	—	—	—

[a] Experimental values, 60 MHz; [b] experimental values, 100 MHz; [c] calculated by independent methods (see the text).

Adamantanone (I). The relative distances of the various protons in the adamantanone molecule are given in Table I, for the case of the gadolinium–oxygen distance of 0·26 nm. Table II presents the absolute distances as calculated by means of the programs GDZPR and GDZPR 1. From the value of the optimization criterion one cannot decide, which of the coordination models (coordination to one or to two molecules of the relaxation reagent) is more correct for this compound. We can therefore use the simpler model GDZPR, *i.e.* the concept of coordination of a single $Gd(DPM)_3$ molecule to the carbonyl group, with the Gd atom lying on the X-axis on the prolonged connecting line C—O in the distance of approximately 0·26 – 0·27 nm from the oxygen atom. It should be borne in mind that (in this and in all other cases) this does not mean a static position, but a time-averaged (effective) one. If the program GDZPR 2 is used (assumption of coordination of two $Gd(DPM)_3$ molecules and the gadolinium atoms in the X – Z plane), the optimization criterion attains values as high as ~0·4 and, in addition, the calculated sites of the two Gd atoms lie very close to one another, which is impossible for steric reasons; thus this model is obviously incorrect – in fact, there is no ground for the assumption of the coordination in the X – Z plane.

2-*Oxaadamantane* (II). The relative distances are given in Table I. In this case the comparative values were measured on Dreiding models assuming the Gd atom to lie on the X-axis in the distance of 0·28 nm from the oxygen atom. The results of calculations of the absolute distances employing the program GDZPR are given in Table II. The value of the optimization criterion is lower than that for the calculation according to the program GDZPR 2 (Table II), where in addition, the obtained

TABLE II

Results of Calculations Using the Computer Programs

Compound		GDZPR		GDZPR1 and GDZPR2		
		distance[c], nm	P_{v_i}[d]	distance[c], nm	angle, deg	P_{v_i}[d]
I	*a*	0·269 ± 0·005	0·24	0·407 ± 0·019	50·5 ± 2·4[e]	0·24
	b	0·258 ± 0·019	0·20	0·376 ± 0·065	53·6 ± 4·3[e]	0·15
II	*a*	0·303 ± 0·082	0·05	0·325 ± 0·048	83 ± 31[f]	0·11
	b	0·485 ± 0·058	0·25	0·358 ± 0·099	83 ± 14[f]	0·11
III	*a*	0·371 ± 0·014	0·48	0·462 ± 0·008	42·4 ± 3·6[f]	0·05
	b	0·410 ± 0·070	0·47	0·460 ± 0·047	42·9 ± 8·8[f]	0·04

[a] At 60 MHz; [b] at 100 MHz; [c] distance of the Gd atom from the origin of the coordinate system; [d] average value of the optimization criterion; [e] angle ψ in the $x-y$ plane, calculation with the program GDZPR1; [f] angle φ in the $x-z$ plane, calculation with the program GDZPR2.

distance between the two coordination sites is again unreasonably short. The assumption of coordination of the compound *II* to a single molecule of $Gd(DPM)_3$ is therefore more correct. From the calculations according to the program GDZPR 1, results of no physical meaning emerge, with the value of the optimization criterion approaching unity.

2,2-*Dioxy*-2-*thiaadamantane* (III). The relative distances are given in Table I and compared with those obtained from the Dreiding models assuming coordination of one molecule of the compound *III* simultaneously to two molecules of $Gd(DPM)_3$, the S—O bond length 0·145 nm and the site of the gadolinium atom on the prolonged connecting line S—O in the distance of 0·25 nm from the oxygen atom. The absolute distances, calculated employing the GDZPR and GDZPR 2 programs, are listed in Table II. Calculations according to GDZPR 1 give meaningless results, with the value of the optimization criterion near unity. Obviously, the most probable is here the coordination of two molecules of $Gd(DPM)_3$ to one molecule of the compound *III*, with the S—O and O—Gd bonds lying probably almost on a straight line in the X–Z plane.

2,6-*Dioxaadamantane* (IV). The relative distances are shown in Table I, the comparative values were calculated by means of the Dreiding models for the coordination of one molecule of the relaxation reagent to each oxygen atom; the sites of the Gd atoms were supposed to lie on the X-axis, 0·3 nm from the respective oxygen atoms. We did not carry out measurements at 100 MHz and calculations of the absolute distances.

2-*Thiaadamantane* (V). When measuring at 60 MHz we were not able to find such a shift reagent, which would enable the relaxation reagent experiments; this is obviously due to a low constant of formation of the complex adduct of the compound *V* with the shift reagents. Measuring at 100 MHz with the shift reagent $Yb(FOD)_3$ we found the signal broadening approximately equal for all protons of the molecule of *V*. Owing to this, very long distances Gd—S emerge from calculations of the absolute distances. We suppose therefore that the relaxation reagent $Gd(DPM)_3$ virtually does not form a complex with the compound *V* and the broadening found is to be ascribed to the nonselective effect.

The relaxation reagent technique can supplement in a simple manner the measurements with shift reagents. For the investigation of the effect of the presence of Gd^{3+} on the line width, the results measured should be considered only semiquantitative, although the calculated positions of Gd^{3+} in the complex adduct are very close to the positions of Eu calculated during shift reagent experiments. This we conclude considering the following facts: *a*) The effect of Gd^{3+} on the broadening appears to the highest extent at the nearest protons; the half widths of the more remote protons change much less and their reading is less accurate. *b*) The competition between the equilibria shift reagent – substrate and relaxation reagent – substrate

can affect the effective position of Gd^{3+} in the complex adduct, owing to the low concentration of the relaxation reagent.

A more detailed image of the potentialities of the application of relaxation reagents for structural analysis will probable emerge from direct measurements of relaxation times[14-18].

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